FORMULATION AND EVALUATION OF SORAFENIB TOSYLATE FILM COATED TABLETS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

Chennai

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

Reg. No. 26101001

Under the guidance of

Dr. GRACE RATHNAM M. Pharm., Ph.D;

Department of pharmaceutics

DEPARTMENT OF PHARMACEUTICS

C.L.BAID MEHTA COLLEGE OF PHARMACY

(An ISO 9001-2000 certified institute)

THORAIPAKKAM, CHENNAI-600097

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CERTIFICATE

This is to certify that the project entitled **"FORMULATION AND EVALUATION OF SORAFENIB TOSYLATE FILM COATED TABLETS"** submitted by **26101001** is a bonafide work carried out by the candidate under my guidance **(Dr. Grace Rathnam, M.Pharm., Ph.D.)** to The TamilNadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment for the degree of Master of Pharmacy in Pharmaceutics, C.L. Baid Metha College of Pharmacy, Chennai, during the academic year 2011-2012.

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DECLARATION

I hereby declare that the dissertation work entitled "**FORMULATION AND EVALUATION OF SORAFENIB TOSYLATE FILM COATED TABLETS**" Submitted in partial fulfillment for the award of the degree of Master of Pharmacy in Pharmaceutics to The TamilNadu Dr.MGR Medical University, Chennai, was carried out in Natco pharma limited located at Kottur, Hyderabad, under the guidance and supervision of **Dr. GRACE RATHNAM**, **M. Pharm., Ph. D.,** and industrial guide **Mr. AMARNATH, M. Pharm.** I also declare that the matter embodied in it is a genuine work.

Date:

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Place: Chennai

ACKNOWLEDGEMENT

I offer my adoration to **God Almighty** who created me, gave me the strength and courage to complete my dissertation and given me the opportunity to thank all those people through whom this grace was delivered to me.

It is a very exciting and memorable moment for me to express my immense gratitude and sincere thanks to my research guide and the chief architect of this work **Dr. GRACE RATHNAM**, **M. Pharm, Ph.D.,** Department of Pharmaceutics, C.L.BAID METHA COLLEGE OF PHARMACY for appetizing suggestions, thoughts provoking discussions, and morale boosting advises. I also owe special debt of gratitude to my research guide for her rich expertise's and encouragement throughout the research work for its successful denouncement and helping in preparing and completion of this dissertation.

I owe a special word of thanks to my industrial guide, **Mr.AMARNATH**, **M. Pharm;** Head of Formulation and Development, NATCO PHARMA LIMITED, for his advice and overall supervision of my project work.

I am thankful to **Mr.Venkateswararao, Mr.Ramakrishna, Mr.Chaitanya Kumar and Mr.Balakrishna** of Formulation and Development, Natco Pharma Limited for their keen interest to teach me all the basics of formulation development along with timely support and motivation and their extended cooperation.

I again thank all those who were involved in my accomplishments directly or indirectly.

Date:

Place: Chennai **Reg. No. 26101001**

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ABBREVIATIONS

µm	Micrometer
µl	Micro liter
GMP	Good Manufacturing Practices
USP	United States Pharmacopeia
mg	Milligram
Gm	Gram
API	Active Pharmaceutical Ingredient
DT	Disintegration time
ND	Not detected
Rpm	Rotations per minute
MCC	Microcrystalline Cellulose
SLS	Sodium lauryl sulphate
CCS	Crosscarmellose sodium
SSG	Sodium starch glycolate
Min	Minute
ºC	Degree Celsius
C max	Maximum Concentration
T max	Maximum Time
Ppm	Parts per million
RMG	Rapid Mixer Granulator
FBP	Fluid Bed Processor
Cfu/g	Colony forming unit/gram
APAP	Acetaminophen
PDGFR	Platelet Derived Growth Factor
FLT	Flutamide
MC	Moisture Content
LOD	Loss on drying
RSD	Relative Standard Deviation
NCE	New Chemical Entity
RCC	Renal Cell Carcinoma
Vhl	Von hippel landau genes

Hprc	Hereditary papillary renal carcinoma
Fro	Familial renal oncocytoma
BHDS	Birt-Hogg-Dude Syndrome
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular Endothelial Growth Factor Receptor
EGFR	Epidermal Growth Factor
MAPK	Mitogen Activated Protein Kinase
HCC	Hepato Cellular Carcinoma
λ_{max}	Absorption maximum

Oral solid dosage forms:

A solid dosage form is a drug delivery system that includes tablets, capsules, sachets and pills as well as a bulk or unit-dose powders and granules. Among the various dosage forms oral solid dosage forms have greater importance and occupy a prime role in the pharmaceutical market. Oral route of drug administration is widely acceptable and drugs administered orally as solid dosage form represents the preferred class of products. Over 90% of drugs formulated to produce systemic effects are produced as solid dosage forms. Because of this reason, whenever new chemical entity (NCE) has discovered, which shows a sufficient pharmacological action, first the pharmaceutical company asks whether the drug is successfully administered by oral route or not. The oral route of administration still continues to be the most preferred route due to its manifold advantages including:

- Tablets and capsules represent unit dosage forms in which the accurate dose of drug to show sufficient pharmacological action can be administered. In case of liquid oral dosage forms such as syrups, suspensions, emulsions, solutions and elixirs the patient is asked to administer the medication of 5-30 ml. Such dosage measurements are typically error by factor ranging from 20-50 %, when the drug is self administered by patient.
- Solid dosage forms are less expensive to shipping and less prone for the degradation when compared to liquid dosage forms.
- Liquid dosage forms are less potable and require more space in pharmacist's shelf. Drugs are generally less stable in liquid form.

Tablets:

Tablets are defined as solid preparations each containing a single dose of one or more active ingredients and obtained by compressing uniform volumes of particles. They are intended for oral administration, they can be swallowed whole, chewed, dispersed in water before being administered or retained in the mouth. Tablets are used mainly for systemic drug delivery but also for local drug action. For systemic use drug must be released from tablet that is dissolved in the fluids of mouth, stomach and intestine and then absorbed into systemic circulation by which it reaches its site of action. Tablets are

usually right, circular solid cylinders, the end surfaces of which are flat or convex and the edges of which may be beveled and may be coated. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

Advantages of tablets

- They are easy to administer.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.

Disadvantages of tablets:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter tasting drugs, drugs with objectionable odor or drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or a special type of coating which may increase the weight of the finished products [1,2].

Types of tablets

The main reasons behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process. To understand each dosage form, tablets here are classified by their route of administration and by the type of drug delivery system they represent within that route.

A. Tablets ingested orally:

1. Compressed tablet
2. Multiple compressed tablet
3. Repeat action tablet
4. Delayed release tablet, e.g. Enteric coated Bisacodyl tablet
5. Sugar coated tablet, e.g. Multivitamin tablet
6. Film coated tablet, e.g. Metronidazole tablet
7. Chewable tablet, e.g. Antacid tablet

B. Tablets used in oral cavity:

1. Buccal tablet, e.g. Vitamin-C tablet
2. Sublingual tablet, e.g. Glyceryl tri nitate tablets
3. Troches or lozenges e.g. Vicks Menthol tablet
4. Dental cone

C. Tablets administered by other route:

1. Implantation tablet
2. Vaginal tablet, e.g. Clotrimazole tablet

D. Tablets used to prepare solution:

1. Effervescent tablet, e.g. Dispirin tablet (Aspirin)
2. Dispensing tablet, e.g. Enzyme tablet (Digiplex)
3. Hypodermic tablet
4. Tablet triturates e.g. Enzyme tablet (Digiplex)

A. Tablets ingested orally:

1. Compressed tablets: Standard uncoated tablets are manufactured by compression. The general methods are by wet granulation, dry granulation or direct compression, used for rapid disintegration and drug release. Both type of action – systemic effect and local effect.

2. Multiple Compressed tablets: For incompatible components these are formulated in two ways:

a. Layered tablet- These are either two layered (for two components) or three layered (for three components) tablets.

b. Compressed coated tablet- These are either tablet within a tablet or tablet within a tablet within a tablet. Tablet in this category are usually prepared for two reasons

1. To separate physically or chemically incompatible ingredients.
2. To produce repeat action or prolong action product.

3. Repeat action tablet: Sugar coated or multiple compressed tablets are used for this purpose. The core tablet is usually coated with Shellac or an enteric polymer so that it will not release its drug in stomach but intestine.

4. Delayed action and Enteric-coated tablet: This dosage form is intended to release the drug after some time delay or after the tablet has passed one part of the GIT into another. All Enteric coated tablets are type of Delayed action tablet but all Delayed action tablets are not Enteric or not intended to produce enteric action.

5. Sugar coated tablet: Primary role of Sugar coating is to produce an elegant, glossy tablets. These are easy to swallow and widely utilized in preparing multivitamin and multivitamin mineral combination. Sugar coating doubled the tablet weight. Now polymers are used with sugar solution.

6. Film coated tablet: One type of coated tablet in which drug is not required in coating. This is an attractive method within one or two hours. Polymers such as Hydroxypropylcellulose, Hydroxypropylmethyl cellulose, and colloidal dispersion of Ethylcellulose are commonly used. A 30% dispersion of Ethyl cellulose, is known as Aquacoat, is widely used in film coating. Advantage of film coated over sugar coated tablets is better mechanical strength and flexibility of the coating, little increase in tablet weight.

7. Chewable tablet: These are intended to be chewed in the mouth before swallowing. Used for large tablet of antacid. Bitter or foul testing drugs are not suitable for this type tablet.

B. Tablets used in oral cavity:

1. **Buccal and sublingual tablet**: These tablets are small, flat and are intended to be held between the cheek and teeth or in cheek pouch (buccal tablet) or below the tongue (sublingual tablet). Drugs used by this route are for quick systematic action. The tablets are designed not to be disintegrated but slowly dissolve.

2. Troches and lozenges: These are used in the oral cavity to exert local effect in mouth and throat. They are commonly used to treat sore throat or to control coughing in common cold. They may contain local anesthetics, antiseptic, antibacterial agents, demulcents, astringent and anti tussive. These tablets are dissolving slowly over a period of 30 minutes.

3. Dental cone: These tablets are designed to be placed in the empty socket remaining after tooth extraction. Main purpose is to prevent microbial growth in the socket or to reduce bleeding.

C. Tablets administered by other route:

1. Implantation tablets: These tablets are designed for substances implantation to provide prolonged drug effect from one month to a year; tablets are usually small, cylindrical not more than 8mm length. These methods require special surgical technique for implantation and discontinuation of therapy. Generally used for administration of growth hormone to food producing animal.

2. Vaginal tablets: These are designed to undergo slow dissolution and drug release in vaginal cavity. Tablets are wide or pear shaped, used to produce antibacterial, antiseptic and astringent effects to treat vaginal infection.

D. Tablets used to prepare solution:

1. Effervescent tablets: Tablets are designed to produce a solution rapidly with the release of carbon dioxide. The tablets are prepared by compressing the active ingredient with mixture of organic acid such as Citric acid and Sodium bicarbonate.

2. Dispersing tablets: Tablets are intended to be added to a given volume of water to produce a solution of a given drug concentration.

3. Hypodermic tablets: These tablets are composed of one or more drugs with water-soluble ingredients. Drug is added to sterile water to prepare sterile solution, which is injectable.

4. Tablet triturates: Usually these are made from moist materials using a triturate mold, which gives them the shape of cylinder. Generally these tablets consist of highly potent drugs [3].

Current technologies in oral drug delivery:

Over the last three decades, many novel oral drug therapeutic systems have been invented along with the appreciable development of drug delivery technology. Although these advanced drug delivery systems are manufactured or fabricated in traditional pharmaceutical formulations, such as tablets, capsules, sachets, suspensions, emulsions, and solutions, they are superior to the conventional oral dosage forms in terms of their therapeutic efficacies, toxicities, and stabilities.

Based on the desired therapeutic objectives, oral drug delivery system may be assorted into three categories:

- Immediate-release preparations,
- Controlled-release preparations and
- Targeted- release preparations.

Immediate-Release Preparations (IR):

These preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability through transmucosal delivery and pregastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and new business opportunities.

Conventional immediate release (IR) formulations include fast disintegrating tablets and granules that use effervescent mixtures, such as sodium carbonate (or sodium bicarbonate) and citric acid (or tartaric acid), and superdisintegrants, such as sodium starch glycolate, croscarmellose sodium, and crospovidone. Current technologies in fast-dispersing dosage forms include modified tableting systems, floss or shear form technology, which employs application of centrifugal force and controlled temperature, and freeze-drying.

Controlled-Release Preparations (CR):

The currently employed controlled release (CR) technologies for oral drug delivery are diffusion-controlled systems; solvent activated systems, and chemically controlled systems. Diffusion-controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate-limiting step, respectively, through a polymer matrix or a polymeric membrane. Solvent-activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain. It is worth mentioning here that the so-called programmed-release (‘‘tailored-release’’) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending on the specific physicochemical properties of the drug in question and desired therapeutic objectives, different formulation and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate desired principles.

Targeted-Release Preparations:

Site-specific oral drug delivery requires spatial placement of a drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site-specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The latter requires consideration of both longitudinal and transverse aspects of GI constraints.

Method of Tablet Preparation:

There are three general methods of tablet preparation.

A. Direct compression method.

B. Wet granulation method.

C. Dry granulation method.

A. Direct Compression method: In this method drug was accurately weighed and mixed thoroughly with excipients (which are directly compressible) by geometrical mixing method. The resultant mixture was compressed into tablet using tablet punching machine.

Commonly used directly compression diluents are: MCC (Microcrystalline cellulose (Avicel), Spray dried lactose, Starch - (Sta Rx 1500, Embdex, Celutab), Sugar

(Sugartab, Nutab), Dicalcium phosphate dihydrate (Di-Tab), Mannitol for chewable tablet.

Steps involved in Direct Compression method:

Raw material → Weighing → Screening → Mixing → Compression

The ideal requirements of excipients used in direct compression and its advantages, limitations are as follows:

Table 1: Ideal requirements& advantages & limitations of direct compression

Ideal Requirement	**Advantages**	**Limitations**
Flowability	Cost effectiveness production	Segregation
Compressibility	Better stability of drug	Variation in functionality
Dilution potential	Faster dissolution	Low dissolution potential
Stability	Simplified validation	Poor compressibility of drug
Controlled particle size	Less microbial contamination	Lubricant sensitivity

Granulation:

Granulation may be defined as a size enlargement process which converts small particles into physically stronger & larger agglomerates. Granulation method can be broadly classified into three types:

- **Wet granulation**
- **Dry granulation**
- **Dry Granulation incorporating bound moisture (MADG)**

Ideal characteristics of granules:

The ideal characteristics of granules include uniformity, good flow, and compatibility. These are usually accomplished through creation of increased density, spherical shape,

narrow particle size distribution with sufficient fines to fill void spaces between granules, adequate moisture (between 1-2%), and incorporation of binder, if necessary.

Wet granulation: The concept of wet granulation is well-known and conventional process for tablet formation, used to reduced bitterness of active drug with water insoluble materials. In wet granulation, the material to be granulated, usually in powder forms, is wetted with an aqueous composition of a granulating agent to cause the powdered material to agglomerates. This agglomerated product is subsequently dried and then milled to reduced size in suitable form.

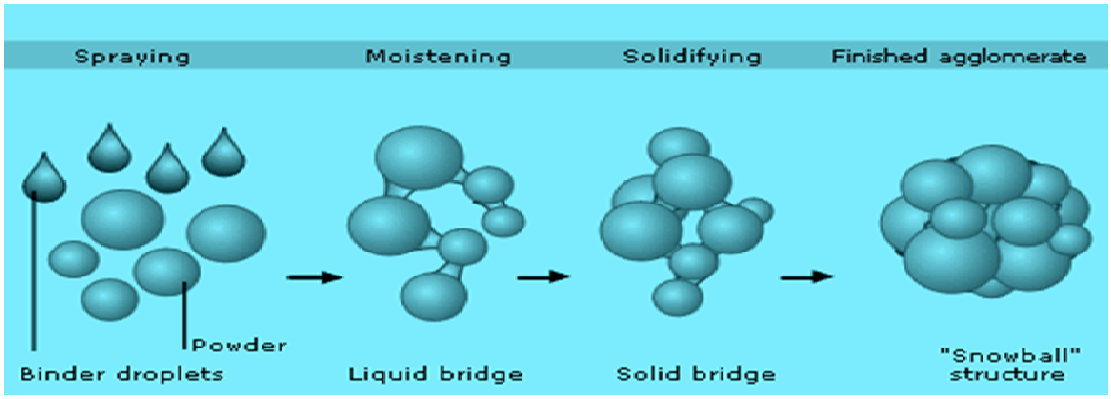


Fig. 1: Process principle for formation of agglomerates

Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over-wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables. Hence, additional process monitoring techniques would be valuable.

Important steps involved in wet granulation:

Raw materials → Weighing → Screening → Wet massing → Sieving/Milling → Drying → Screening → Mixing → Compression.

1) Mixing of drug(s) and excipients.
2) Preparation of binder solution.
3) Mixing of binder solution with powder mixture to form wet mass.
4) Coarse screening of wet mass using a suitable sieve (6-12 screens).
5) Drying of moist granules.
6) Screening of dry granules through a suitable sieve (14-20 screens).
7) Mixing of screened granules with disintegrant, glidant and lubricant.

Limitations of wet granulation:

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing.
- Stability may be a major concern for moisture sensitive or thermolabile drugs.
- Multiple processing steps give complexity and make validation and control difficult.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

Dry granulation:

In Dry granulation process the powder mixture is compressed without the use of heat and solvent. It is the least desirable of all methods of granulation. The two basic procedures are to form a compact of material by compression and then to mill the compact to obtain a granules. Two methods are used for dry granulation. The more widely used method is Slugging, where the powder is pre-compressed and the resulting tablets or slugs are milled to yield the granules. The other method is to pre-compress the powder with pressure rolls using a machine such as Chilosonator.

Steps in Dry granulation:

Raw material → weighing → Screen → Mixing → Slugging → Milling → Screening → Mixing → Compression

1) Milling of drugs and excipients

2) Mixing of milled powders

3) Compression into large, hard tablets to make slug

4) Screening of Slugs

5) Mixing with lubricant and disintegrating agent

6) Tablet compression

Two main dry granulation processes:

Slugging process:

Granulation by Slugging is the process of compressing dry powder of tablet formulation with tablet press having die cavity large enough in diameter to fill quickly. The accuracy or condition of slug is not too important. Only sufficient pressure to compact the powder into uniform slugs should be used. Once slugs are produced they are reduced to appropriate granule size for final compression by screening and milling.

Roller compaction:

The compaction of powder by means of pressure roll can also be accomplished by a machine called chilsonator. Unlike tablet machine, the chilsonator turns out a compacted mass in a steady continuous flow. The powder is fed down between the rollers from the hopper which contains a spiral auger to feed the powder into the compaction zone. Like slugs, the aggregates are screened or milled for production into granules.

Procedure for Dry granulation method

The excipients used for dry granulation are basically same as that of wet granulation or that of direct compression. With dry granulation it is often possible to compact the active ingredient with minor addition of lubricant and disintegrating agent. Fillers that are used in dry granulation include the following examples: Lactose, Dextrose, Sucrose, Microcrystalline cellulose, Calcium sulphate etc.

Advantages:

The main advantages of dry granulation or slugging are that it uses less equipment and space. It eliminates the need for binder solution, heavy mixing equipment and the costly and time consuming drying step as required in wet granulation. Slugging can be used for advantages in the following situations:

I. For moisture sensitive material.

II. For heat sensitive material.

III. For improved disintegration since powder particles are not bonded together by a binder.

Disadvantages:

1) It requires a specialized heavy duty tablet press to form slug.

2) It does not permit uniform color distribution.

3) Achieved with wet granulation where the dye can be incorporated into binder liquid.

4) The process tends to create more dust than wet granulation, increasing the potential contamination [4,5,6].

Further, excipients are used also used in tablet manufacturing which are inert substances used as diluents or vehicles for a drug. The screening of drug-excipient and excipient-excipient interactions should be carried out routinely in pre formulation studies [7].

Tablet Coating:

The coating can have several functions. It can strengthen the tablet, control its release, improve its taste, color it, makes it easier to handle and package, and protect it from moisture. All drugs have their own characteristic, like some drugs are bitter in taste or have an unpleasant odor, some are sensitive to light or oxides, some are hygroscopic in nature, which can be altered by coating. Sugar coating was carried out initially which was now replaced by film coating.

Tablet film coating is performed by two types, one is aqueous film coating generally water is used as a solvent) and non aqueous film coating (generally organic solvent are used). High quality aqueous film coating must be smooth, uniform and adhere satisfactorily to the tablet surface and ensure chemical stability of a drug, where as it need permission from the regulatory authority since organic solvents are used.

Reasons for Tablet Coating:

A number of reasons can be suggested:

The core contains a material which has a bitter taste in the mouth or has an unpleasant odour, enhance the elegance, increase the mechanical integrity and stability.

The coated tablets can be packed on high-speed packaging machine. Coating reduces friction and increases packaging rate.

Coating can modify the drug release profile, e.g., enteric coating, osmotic pump, pulsatile delivery [8,9].

Film Coating Materials:

A film coating is a thin polymer-based coat applied to a solid dosage form such as a tablet. The thickness of such a coating is usually between 20-100 µm. Under close inspection the film structure can be seen to be relatively non- homogenous and quite distinct in appearance, from a film forming, from casting a polymer solution on a flat surface.

Film coating formulations usually contain the following components:

1. Polymer
2. Plasticizer
3. Colourants / Opacifiers
4. Solvent / Vehicle.

1. Polymer

Among the vast majority of the polymers used in film coating are cellulose derivatives or acrylic polymers and copolymers.

Non-enteric polymers:

Hypromellose, Hydroxy ethyl cellulose, Hydroxy ethyl methyl cellulose, Carboxy methyl cellulose sodium, Hydroxy propyl cellulose, Polyethylene glycol, Ethylcellulose

Enteric polymers:

Hypromellose phthalate, Polyvinyl acetate phthalate, Cellulose acetate phthalate

Polymethacrylates, Shellac

2. Plasticizers

Plasticizers are simply relatively low molecular weight materials which have the capacity to alter the physical properties of the polymer to render it more useful in performing its function as a film coating material. Plasticizers are classified in three groups. Polyos type contains glycerol, propylene glycol, PEG (Polyethylene glycol).

Organic esters contain phthalate esters, dibutyl sebacetate, citrate esters, triacetin. Oils/glycerides contain castor oil, acetylated, monoglycerides, and fractionated coconut oil.

3. Solvents/Vehicles

The key function of a solvent system is to dissolve or disperse the polymers and other additives. The major classes of solvents being used are

- Water
- Alcohols
- Ketones
- Esters
- Chlorinated hydrocarbons

Because of environmental and economic considerations, water is the solvent of choice; however organic coating is totally cannot be avoided.

4. Colourants / Opaquants:

These materials are generally used as ingredients in film-coating formulae to contribute to the visual appeal of the product, but they also improve the product in other ways:

- Identification of the product by the manufacturer and therefore act as an aid for existing GMP procedures.
- Reinforcement of brand imaging and reduction in product counterfeiting.
- Identification of the product by patients by using colourants and to prevent decomposition from exposure to light.

Colourants are mainly classified in to three classes. Sunset yellow, Tartrazine, Erythrosine are examples of organic dyes and their lakes. Iron oxide yellow, red and black, Titanium dioxides, Talc are the examples of Inorganic colours. Anthrocyanins, Ribofloavine and Carmine are the examples of natural colours.

Miscellaneous coating solution components:

To provide a dosage form with a single characteristic, special materials may be incorporated into a solution.

Flavours and sweeteners are added to mask unpleasant odours or to develop the desired taste. For example, Aspartame, various fruit spirits (organic solvent), water soluble pineapple flavor (aqueous solvent) etc.

Surfactants are supplementary to solubilize immiscible or insoluble ingredients in the coating. For example, Spans, Tweens etc.

Antioxidants are incorporated to stabilize a dye system from oxidation and colour change. For example Oximes, Phenols etc.

Antimicrobials are added to put off microbial growth in the aqueous coating composition which is prone for microbial growth. Ex. Alkyl iso thiazloinone, Carbamates, Benzothiazoles etc [10,11].

Coating Process:

Film-coating of tablets is a multivariate process, with many different factors, such as coating equipment, coating liquid, and process parameters which affect the pharmaceutical quality of the final product. Coating liquid used in the may affect the final quality of the tablets. Different film former have different chemical nature and different characteristics. Percentage Solid content generally affects the tablet surface and coating efficiency [12]. Process parameters such as spray rate, atomizing air pressure, inlet air temperature and rotating speed of the fan also influences the coating. Optimization of the above said parameters results in the formation of a proper film, whereas improper spraying or altered air pressure, temperature and fan speed result in sticking of film, reduced tablet porosity, attrition and breakage [13,14,15].

Cancer:

Cancer is a class of diseases characterized by out-of-control cell growth. There are over 100 different types of cancer, and each is classified by the type of cell that is initially affected.

Etiology of cancer:

Normal cells in the body follow an orderly path of growth, division, and death. Programmed cell death is called apoptosis, and when this process breaks down, cancer begins to form. Unlike regular cells, cancer cells do not experience programmatic death

and instead continue to grow and divide. This leads to a mass of abnormal cells that grows out of control.

Classification:

There are five broad groups that are used to classify cancer.

1. Carcinomas are characterized by cells that cover internal and external parts of the body .such as lung, breast, and colon cancer.

2. Sarcomas are characterized by cells that are located in bone, cartilage, fat, connective tissue, muscle, and other supportive tissues.

3. Lymphomas are cancers that begin in the lymph nodes and immune system tissues.

4. Leukemias are cancers that begin in the bone marrow and often accumulate in the bloodstream.

5. Adenomas are cancers that arise in the thyroid, the pituitary gland, the adrenal gland, and other glandular tissues.

Diagnosis:

Physicians use information from symptoms and several other procedures to diagnose cancer. Imaging techniques such as X-rays, CT scans, MRI scans, PET scans, endoscopy and ultrasound scans are used regularly to detect where a tumor is located and what organs may be affected by it. Biopsies and various bio marker tests were also used to detect specific cancers, For example; cancerous prostate cells release a higher level of a chemical called PSA (prostate-specific antigen) into the bloodstream that can be detected by a blood test.

Treatment:

Cancer treatment depends on the type of cancer, the stage of the cancer (how much it has spread), age, health status, and additional personal characteristics. There is no single treatment for cancer, and patients often receive a combination of therapies and palliative care. Treatments usually fall into one of the following categories: surgery, radiation, chemotherapy, biological therapy, hormone therapy or gene therapy.

Renal cell carcinoma:

Renal cell carcinoma (RCC, also known as Hypernephroma) is a cancer occurring in kidney that originates in the lining of the proximal convoluted tubule. RCC is the most common type of kidney cancer in adults, responsible for approximately 80% of cases. It is also known to be the most lethal of all the genitourinary tumors. Metastatic renal cell carcinoma presents a special challenge to oncologists, as about 70% of patients develop metastases during the course of their disease [16].

Prognosis of Renal cell carcinoma:

The staging of renal cell carcinoma is the most important factor in predicting its prognosis. Staging can follow the TNM staging system, where the size and extent of the tumour (T), involvement of lymph nodes (N) and metastases (M) are noted.

Stage I: Tumor of a diameter of 7 cm (approx. 2¾ inches) or smaller, and limited to the kidney. No lymph node involvement or metastases to distant organs.

Stage II: Tumor larger than 7.0 cm but still limited to the kidney. No lymph node involvement or metastases to distant organs.

Stage III: Tumor of any size with involvement of a nearby lymph node but no metastases to distant organs. Tumor of this stage may be with or without spread to fatty tissue around the kidney, with or without spread into the large veins leading from the kidney to the heart. Tumor with spread to fatty tissue around the kidney and/or spread into the large veins leading from the kidney to the heart, but without spread to any lymph nodes or other organs.

Stage IV: Tumor that has spread directly through the fatty tissue and the fascia ligament-like tissue that surrounds the kidney. Involvement of more than one lymph node near the kidney and or lymph node not near the kidney which are distant metastases, such as in the lungs, bone, or brain.

Pathophysiology:

The tissue of origin for renal cell carcinoma (RCC) is the proximal renal tubular epithelium. Renal cancer occurs in a sporadic (nonhereditary) and a hereditary form, and both forms are associated with structural alterations of the short arm of chromosome 3. Genetic studies of the families at high risk for developing renal cancer led to the cloning of genes whose alteration results in tumor formation. These genes are either tumor suppressors (VHL, TSC) or oncogenes (MET).

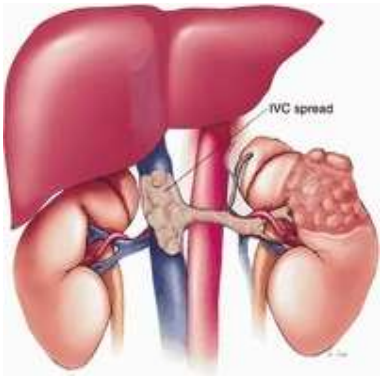


Fig. 2: Proliferation of tumours in Kidneys

At least 4 hereditary syndromes associated with renal cell carcinoma are recognized:

1. Von Hippel-Lindau (VHL) syndrome,
2. Hereditary papillary renal carcinoma (HPRC),
3. Familial renal oncocytoma (FRO) associated with Birt-Hogg-Dube syndrome (BHDS)
4. Hereditary renal carcinoma (HRC).

Von Hippel-Lindau syndrome

It is an autosomal dominant syndrome that confers predisposition to a variety of neoplasms, including the following:

a) Renal cell carcinoma with clear cell histologic features
b) Pheochromocytoma
c) Pancreatic cysts and islet cell tumors
d) Endolymphatic sac tumors

Renal cell carcinoma develops in nearly 40% of patients with von Hippel-Lindau disease and is a major cause of death among these patients. Deletions of 3p occur commonly in renal cell carcinoma associated with von Hippel-Lindau disease. The VHL gene is mutated in a high percentage of tumors and cell lines from patients with sporadic (nonhereditary) clear cell renal carcinoma. Several kindreds with familial clear cell carcinoma have a constitutional balanced translocation between 3p and either chromosome 6 or chromosome 8. Mutations of the VHL gene result in the

accumulation of hypoxia inducible factors (HIFs) that stimulate angiogenesis through vascular endothelial growth factor (VEGF) and its receptor (VEGFR). VEGF and VEGFR are important new therapeutic targets.

Hereditary papillary renal carcinoma

Hereditary papillary renal carcinoma is an inherited disorder with an autosomal dominant inheritance pattern; affected individuals develop bilateral, multifocal papillary renal carcinoma. Germline mutations in the tyrosine kinase domain of the MET gene have been identified.

Familial renal oncocytoma and Birt-Hogg-Dube syndrome

Individuals affected with familial renal oncocytoma can develop bilateral, multifocal oncocytoma or oncocytic neoplasms in the kidney. Birt-Hogg-Dube syndrome is a hereditary cutaneous syndrome. Patients with Birt-Hogg-Dube syndrome have a dominantly inherited predisposition to develop benign tumors of the hair follicle (ie, fibrofolliculomas), predominantly on the face, neck, and upper trunk, and these individuals are at risk of developing renal tumors, colonic polyps or tumors, and pulmonary cysts.

Hereditary renal carcinoma

Affected individuals with this inherited medical condition have an increased tendency to develop oncocytomas, benign kidney tumors that have a low malignant potential.

Etiology:

A number of environmental and genetic factors have been studied as possible causes for renal cell carcinoma (RCC), such as the following:

Cigarette smoking doubles the risk of renal cell carcinoma and contributes to as many as one third of all cases. The risk appears to increase with the amount of cigarette smoking in a dose-dependent fashion.

Obesity and hypertension are the associated risk factor, particularly in women; increasing body weight has a linear relationship with increasing risk.

Phenacetin-containing analgesia taken in large amounts may be associated with increased incidence of renal cell carcinoma.

In renal transplant recipients, acquired renal cystic disease of the native kidney also predisposes to renal cell cancer.

Von Hippel-Lindau disease is an inherited disease associated with renal cell carcinoma.

Hepatocellular carcinoma

Hepatocellular carcinoma is cancer of the liver.

Causes, incidence and risk factors

Hepatocellular carcinoma accounts for most liver cancers. This type of cancer occurs more often in men than women. It is usually seen in people of age 50 years or older and is common in Africa and Asia than in North or South America and Europe.

Hepatocellular carcinoma is not the same as metastatic liver cancer, which starts in another organ (such as the breast or colon) and spreads to the liver.

In most cases, the cause of liver cancer is usually scarring of the liver (cirrhosis). Cirrhosis may be caused by:

- Alcohol abuse (the most common cause in the United States)
- Autoimmune diseases of the liver
- Hepatitis B or C virus infection
- Inflammation of the liver that is long-term (chronic)
- Iron overload in the body (hemochromatosis)
- Patients with hepatitis B or C are at risk for liver cancer, even if they have not developed cirrhosis.

Symptoms

- Abdominal pain or tenderness, especially in the upper-right part
- Easy bruising or bleeding
- Enlarged abdomen
- Yellow skin or eyes (jaundice)

Signs and tests

Physical examination may show an enlarged, tender liver.

Tests include:

- Abdominal enzymes (liver function tests)
- Liver MRI
- Serum alpha fetoprotein
- CT scan
- Abdominal ultrasound
- Liver biopsy

Complications

- Gastrointestinal bleeding
- Liver failure
- Spread (metastasis) of the cancer

Treatment

Aggressive surgery or a liver transplant can successfully treat small or slow-growing tumors if they are diagnosed early. Radiation treatment and chemotherapy delivered straight into the liver with a catheter can help, but it will not cure the disease. However, many patients have liver cirrhosis or other liver diseases that make these treatments more difficult.

Sorafenib:

Sorafenib, a protein kinase inhibitor, approved by FDA in December 2005 for treatment of advanced renal cell carcinoma and hepato cellular carcinoma.

Mechanism of action in Renal Cell Carcinoma (RCC):

Sorafenib targets the VEGFRs and PRGFR, which are key elements in tumor progression and tumorogenesis. Sorafenib blocks the activation of RAS by the VEGF/PDGF receptors autophosphorylation and the resultant phosphorylation and transactivation to RAF and MEK/ERK. It thereby reduces tumor cell survival while impeding metastasis and tumor cell proliferation [17].

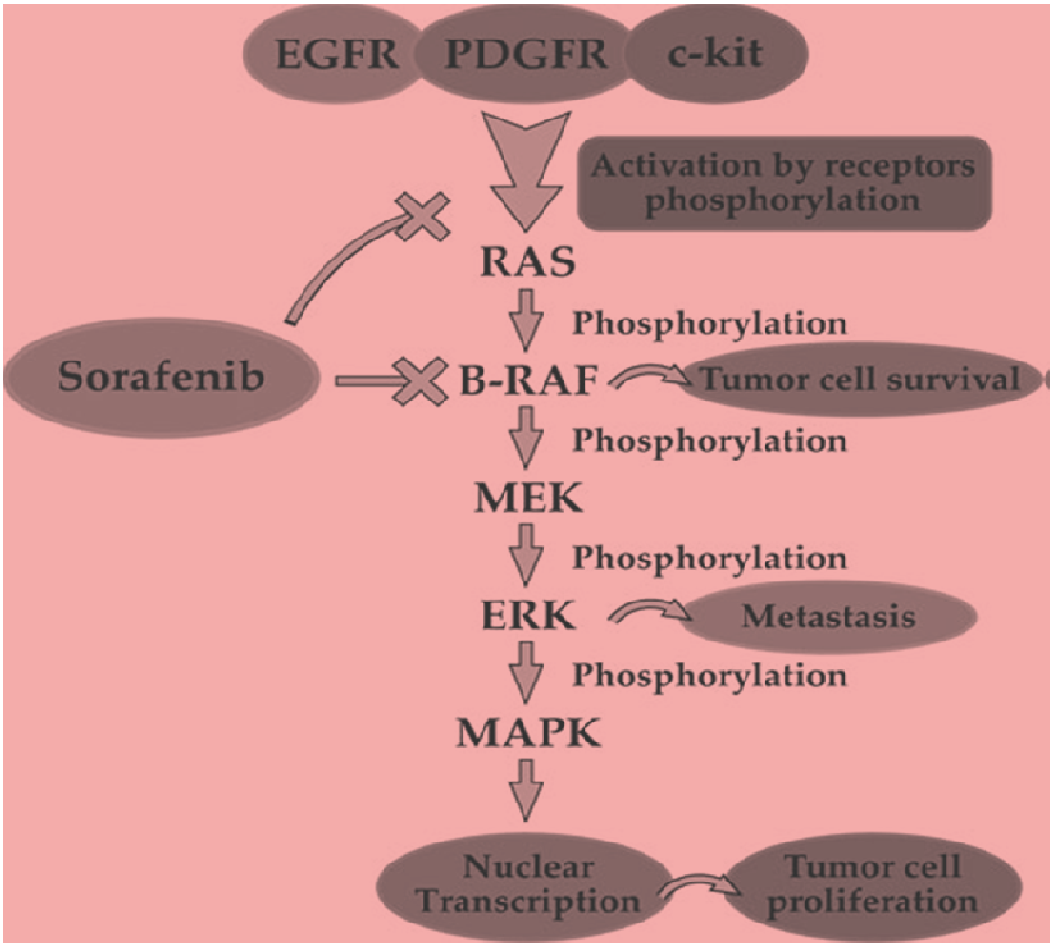


Fig.3: Diagramatic representation of Mechanism of action of (Sorafenib).

Mechanism of action in Hepato Cellular Carcinoma (HCC).

Sorafenib can inhibit the cell proliferation and angiogenesis by inhibiting the threonine and serine kinase system (c-RAF, and mutant and wild-type BRAF). This molecule also inhibits the receptor tyrosine kinases and vascular endothelial growth factor receptor2, 3, platelet derived growth factor receptor (PDGFR), Ret, c-KIT and FLT3, etc. Sorafenib can inhibit the RAF/MEK/ERK pathway both inside and outside the body. It can inhibit the angiogenesis inside the tumor, can develop apoptosis and it is much effective against HCC in humans. In addition to that, the suppression of RAF/MEK/ERK signaling pathway, and the decline in elF4E phosphorylation and

down-regulation of Mcl-1 protein levels may take part in the proapoptotic effects of Sorafenib in human HCC [18].

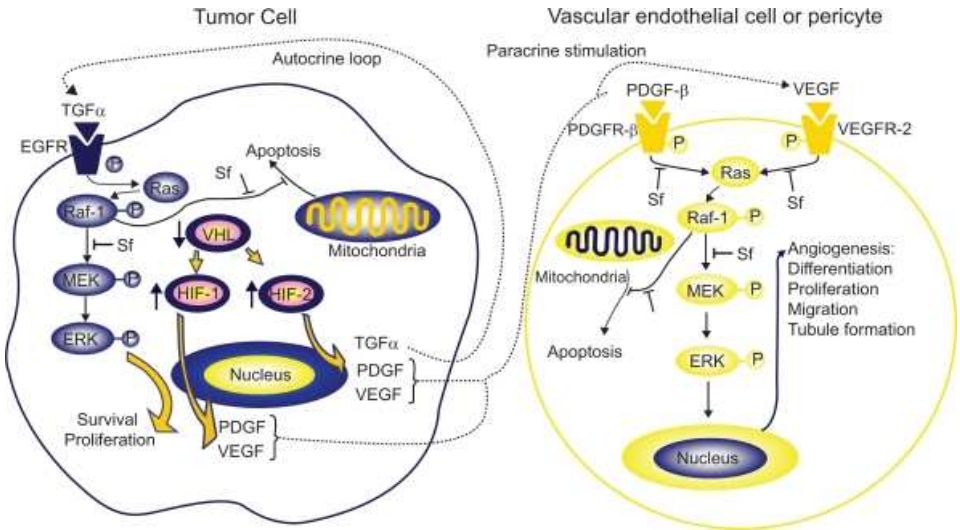


Fig. 4: Diagrammatic representation of mechanism of action of sorafenib.

Reported work on present study:

1. ***Sansonno et al.,* (2012)** carried out a perspective, single center, placebo controlled, randomized, double blind study to evaluate the effectiveness of transarterial chemoembolization (TACE) combined with sorafenib in delaying time to progression (TTP) of intermediate stage HCC in patients with chronic hepatitis C virus infection. At the end of study sorafenib treatment was found to increase the TTP in patients [19].

2. ***Kim et al.,* (2012)** formulated sorafenib incorporated nanoparticles of dextran and poly (DL-lactide-co-glycolide) block copolymer for anti tumor drug delivery. This formulation was found to have a decreased drug release with increasing drug content and anti tumor activity as of sorafenib and thus can be suggested as vehicle for anti tumor drug targeting [20].

3. ***Sacco et al.,* (2011)** reported the effectiveness of the oral multikinase inhibitor sorafenib in Hepatocellular carcinoma (HCC), the fifth most common neoplasia in the world. It was also found that, as like other anti-angiogenic drugs employed in other tumour types, sorafenib also seldom induced the dimensional tumour shrinking usually observed with conventional cytotoxic drugs treatment of advanced HCC [21].

4. ***Ling-lin et al.,* (2011)** evaluated the effectiveness and toxicity of sorafenib for advanced hepatocellular carcinoma. Two Randomized Controlled Trials involving 828 patients were taken for study. Compared with placebo, sorafenib significantly extended the overall survival and time to radiologic progression and improved the disease control rate. The main adverse effects were systemic, gastrointestinal, and dermatologic symptoms (grade 1 or 2 in severity), although the incidences were significantly higher in sorafenib groups than in control groups. Sorafenib was found to be effective and safe for the treatment of advanced hepatocellular carcinoma [22].

5. ***Yuxian Huang et al.,* (2011)** reported that sorafenib and sunitinib are novel small molecule tyrosine kinase inhibitors with multiple targets on tumor cells, which have been demonstrated to be beneficial in the treatment of several carcinomas. Combining the usage of molecular targeted agents and adoptive cellular immunotherapy (ACI) against drug-resistant relapse nasopharyngeal carcinoma which had no standard therapeutic regimen was investigated by them in order to study whether synergistic

effects exist and related mechanisms. The results revealed for the first time that sorafenib and sunitinib could up-regulate NKG2DLs on tumor cells resulting in increased tumor cells cytotoxic sensitivity to NK cells, which suggested that combining usage of molecular targeted agents and ACI may result in great benefits in clinical practice for the therapy-resistant cases and drug-resistant relapse [23].

6. ***Steven Simoens*** **(2011)** conducted a literature review of the dosage and treatment duration; safety, tolerability and effectiveness; costs and cost-effectiveness of sorafenib in routine clinical care. The most common drug-related adverse events were hand-foot skin reaction, rash, hypertension, and fatigue. Although treatment with sorafenib led to fewer dose reductions, it was also associated with shorter treatment duration, less time to pro-gression and a shorter survival time as compared to sunitinib. Monthly health care costs were lower with sorafenib as compared to sunitinib. A post-marketing surveillance study showed that patients rated the tolerability and effectiveness of sorafenib as very good, good or sufficient [24].
7. ***Anton Smith*** **(2011*)*** formulated film coated tablets of secnidazole by wet granulation method and granules are compressed for tablets and they are coated with polymers by using hydroxypropyl methyl cellulose and advatia prime pink. The resulted tablets were evaluated for different parameter and concluded that the coating has not shown any effect on the dissolution of the drug [25].

8. ***Takafumi Kennoki et al.,*** **(2011)** investigated the safety and feasibility of sorafenib in patients with end-stage renal disease undergoing hemodialysis by examining the influence of pharmacokinetic parameters to their benefit and also the occurrence of drug-related adverse events of sorafenib. Treatment with sorafenib in patients with metastatic renal cell carcinoma undergoing hemodialysis appears to be feasible, with higher incidence of serious adverse events without any change in clinical efficacy [26].

9. ***Hong et al.,*** **(2011)** reported the use of sorafenib in patients with advanced renal cell carcinoma who have failed prior cytokine-based therapy are considered unsuitable for such therapy. To find the effectiveness of the drug in real-life practice, an open-label study was observed in patients with stable disease for eight weeks. It was found that the most common drug-related adverse events were hand-foot skin reaction, rash, hypertension, and fatigue. Although treatment with sorafenib led to fewer dose

reductions, it was also associated with shorter treatment duration, less time to progression and a shorter survival time as compared to sunitinib [27].

10. ***Saby George et al.,* (2011)** reported that the first case report of the use of sorafenib and S-1 for the treatment of renal cell carcinoma (RCC) producing granulocyte colony-stimulating factor (G-CSF). This entity is clinically rare and has a poor outcome. A 78-year-old Japanese man presented with macrohematuria, left flank pain, and a palpable mass. Laboratory data showed marked leukocytosis with increased serum and urinary G-CSF. The histopathological diagnosis was unclassified RCC. New combination therapy with sorafenib and S-1 exerted a therapeutic effect and apparently decreased serum and urinary G-CSF levels, although the patient died of gastrointestinal perforation. The use of combined sorafenib and S-1 was suggested to a worthy consideration in the treatment of RCC producing G-CSF [28].

11. ***Wei et al.,* (2011)** investigated the safety and efficacy of sorafenib in combination with chemotherapy for the treatment of FLT3 positive acute myeloid leukemia (AML), to highlight the impact of FLT3 mutations and targeting therapy on response of AML. The clinical and laboratory features and the treatment response, especially the safety profile of sorafenib in an acute monocytic leukemia patient with FLT-ITD were reported. The patient achieved clinical and molecular CR after sorafenib was added to the second course of combination chemotherapy. The side effects of sorafenib were mild and tolerable. The patient responded well to the combination of sorafenib and standard chemotherapy of AML without significant adverse effects [29].

12. ***Wang et al., (2011)*** formulated nanoparticulate-nanomatrix formulation of sorafenib to increase its absorption using porous material sylysia-350 and polymer eudragit. It was found in that study there was a 13-33 times increase in bioavailability in the nano matrix formulation using sylysia nanomatrix and 16.8 to 40.8% in eudragit nano particles [30].

13. ***Duman et al.,* (2011)** reported the efficacy of vit-E treatment in hand foot skin syndrome (HFS) associated with sorafenib treatment. It was found that vit-E had a marked effect on HFS and it decreased the skin lesion without any dose modification of sorafenib [31].

14. ***Li, Huang et al.,* (2010**) reported the more evidence sources to the standard treatment for patients with advanced hepatocellular carcinoma. Parameters such as patient's time to progression (TTP) and overall survival (OS) after patients receiving Transcatheter Arterial Chemo Embolization (TACE) combined with sorafenib as a treatment of advanced hepatocellular carcinoma (HCC), the healing effect embolization combined with anti-angiogenic activity in hepatocellular carcinoma were analysed. The study concluded, TACE combined with sorafenib treatment may give patients with advanced hepatocellular carcinoma a longer longevity and keep the disease in a steady state and can be considered in the treatments to patients with advanced hepatocellular carcinoma [32].
15. ***Ikeda et al.,* (2010)** reviewed the efficacy of sorafenib compared to placebo in hepato cellular carcinoma. Sorafenib demonstrated to yield a significantly favorable disease control rate and also favorable prolongation of progression-free survival and overall survival in patients with advanced hepatocellular carcinoma. Further, use of sorafenib as adjuvant therapy after local treatment, including surgical resection, local ablative therapy and transcatheter arterial chemoembolization for hepatocellular carcinoma were also discussed [33].

16. ***Bengala et al.,* (2010)** reported that use of sorafenib in advanced biliary tract carcinoma which has a very poor prognosis, with chemotherapy being the mainstay of treatment. Sorafenib, a multikinase inhibitor of VEGFR-2/-3, PDGFR-β, B-Raf, and C-Raf, has shown to be active in preclinical models of cholangiocarcinoma [34].

17. ***Benjamin Hagopian, et al.,* (2010)** reported case report details of a patient with an unusually severe and painful skin reaction, in spite there are multiple reports on sorafenib-induced hand foot skin reaction. In this case report, the bullous skin reaction, debilitating hand pain, and absence of foot involvement were reported for the first time [35].

18. ***Kamada et al., (2010*)** reported that targeted therapies used in the treatment of metastatic renal cell carcinoma (RCC) are known to have the potential for cardiotoxicity and should be used with caution in patients with cardiac co morbidities. A retrospective review identified two RCC cases treated with sorafenib in the context of pre existing cardiomyopathy. Sorafenib therapy resulted in disease stabilization of progressing RCC for both cases, without worsening the cardiac ejection fraction [36].

19. ***Degen et al.,* (2010)** evaluated the effect on multiple cutaneous side effects during sorafenib therapy and possible association of epithelial skin cancer growth. The authors reported 2 patients who developed a basal cell carcinoma (BCC) while treated with sorafenib. It was found that, after termination of sorafenib treatment, no new BCCs or other epithelial skin cancers occurred [37].

20. ***Mila Petrova et al.,* (2010)** reported that medullary thyroid cancer (MTC) is a rare and only surgically treatable disease with early development of metastases and bad prognosis. Due to the lack of efficient systemic treatment, new strategies were adopted, such as the use of tyrosine multikinase inhibitors like sorafenib and was effective in patient with metastatic MTC treated for two months [38].

21. ***Hari koul et al.,* (2009)** reviewed the dose-dependent inhibition of cell proliferation and induction of apoptosis seen with sorafenib in human hepatocellular carcinoma cells lines. Sorafenib demonstrated dose-dependent anti tumour activity in a murine xenograft model of human hepatocellular carcinoma. The bi-aryl urea sorafenib (oral multikinase inhibitor) was found to act by inhibiting cell surface tyrosine kinase receptors (e.g. vascular endothelial growth factor receptors and platelet-derived growth factor receptor-beta) and downstream intracellular serine/threonine kinases (e.g. Raf-1, wild-type B-Raf and mutant B-Raf); these kinases are involved in tumour cell proliferation and tumour angiogenesis [39].

22. ***Lettieri et al.,* (2009)** performed a study to assess whether the change of formulation alters the bioavailability of sorafenib. Some patients who are unable to swallow tablets have suspended sorafenib tablets in a liquid for ease of administration. The pharmacokinetics of sorafenib, when administered as a liquid suspension of tablets in water was found to be similar to the pharmacokinetics of tablets swallowed as whole. Further, the use of sorafenib (multikinase inhibitor currently approved by the FDA) for the treatment of advanced renal-cell carcinoma (RCC) and unresectable hepatocellular carcinoma (HCC), and by the EMEA for the treatment of HCC and advanced RCC were also discussed [40].

23. ***Jun-Yan Liu, et al.,* (2009)** reported that sorafenib has epoxide hydrolase (she) inhibitory activity which contributes to its effect profile *in vivo* the advent of multi-kinase inhibitors targeting the VEGF-receptor which revolutionized the treatment of highly angiogenic malignances such as renal cell carcinoma. It was also found that,

several such inhibitors are commercially available, and they each possess diverse specific beneficial and adverse effect profiles. Structural examination of sorafenib, hypothesized that this compound would possess inhibitory effects on the soluble epoxide hydrolase (sEH), an enzyme with pleiotropic effects on inflammation and vascular disease [41].

24. ***Robert Justice et al.,*** **(2009)** exhibited the report of U.S. Food and Drug Administration (FDA) review and approval of sorafenib (Nexavar, BAY43-9006), a new small-molecule, oral, multi-kinase inhibitor for the treatment of patients with advanced renal cell carcinoma (RCC). FDA reviewed the phase 3 protocol under the Special Protocol Assessment mechanism, following new drug application submission, FDA independently analyzed the results of two studies in advanced RCC: a large, randomized, double-blinded, phase 3 international trial of single-agent sorafenib and a supportive phase 2 study [42].

25. ***Wong Michael et al.,*** **(2009)** reported that cardiotoxicity is an emerging concern with a new class of drugs known as targeted agents, which include trastuzumab and sunitinib. Sunitinib is a small molecule that inhibits multiple tyrosine kinase receptors (approved by the United States Food and Drug Administration in 2006) for the treatment of clear cell metastatic renal cell carcinoma and advanced gastrointestinal stromal tumors. It was observed that sunitinib was found to cause heart failure, thus sorafenib, another tyrosine kinase inhibitor, was started with the aim of continuing her previous response to sunitinib. After 7 months of sorafenib therapy, the patient had no evidence of heart failure and concluded the use of sorafenib after sunitinib-induced heart failure appears to be safe and effective, which suggests that cardiotoxicity, is not a general class effect of the tyrosine kinase inhibitors [43].

26. ***Sebastien J Hotte et al.,*** **(2008)** reported a case of adult clear-cell RCC with extensive rhabdoid features treated with the tyrosine kinase inhibitor sorafenib. In this report, Sorafenib appeared to confer prolonged disease stabilization and warrants further study in other rare subtypes of RCC [44].

27. ***Ambrosini et al.,*** **(2008)** reported the possible mechanism my which sorafenib act. When tumor cells were treated with sorafenib, it found to inhibit phospho-MEK, phospho-ERK and cell cycle arrest [45].

28. ***William L. Dahut et al.,*** **(2008)** reported the use of sorafenib in androgen-independent prostate cancer (AIPC). Interpretation of this study is complicated by discordant radiographic and prostate-specific antigen (PSA) responses [46].

29. ***Anil Kapoor et al.,*** **(2008)** reported that renal cell carcinoma (RCC) with rhabdoid features is an uncommon and highly aggressive malignancy. A review of the literature confirms that adult rhabdoid RCC is a rare but aggressive tumour with a distinctly poor prognosis and in their patient, sorafenib appeared to confer prolonged disease stabilization and warrants further study in this and other subtypes of RCC [47].

30. ***Liliana Moreno-Vinasco et al.,*** **(2008)** investigated that pulmonary hypertension (PH) and cancer pathology share growth factor- and MAPK stress-mediated signaling pathways resulting in endothelial and smooth muscle cell dysfunction and angioproliferative vasculopathy. In this study, they reported that, sorafenib, an antineoplastic agent and inhibitor of multiple kinases important in angiogenesis [VEGF receptor (VEGFR)-1–3, PDGF receptor (PDGFR)-β, Raf-1 kinase] as a potential PH therapy [48].

31. ***Gudena, et al.,*** **(2008)** reported tha**t** malignant schwannomas or malignant peripheral nerve sheath tumors (MPNST) represent approximately 10% of all soft tissue sarcomas. Case study of a metastatic disease from chest wall MPNST is very rare and the response to tyrosine kinase inhibitor (TKI) sorafenib in a 42 year female patient with metastatic MPNST was reviewed and it was reported. MPNST show high levels of Ras activity and hence these tumors are promising targets for TKIs studies [49].

33. ***Guan et al.,*** **(2008)** reported that sorafenib is a novel oral bis-aryl urea compound that has proven survival benefit in patients with advanced hepatocellular carcinoma (HCC), for which several therapies are currently available with unsatisfactory results. Sorafenib is the first compound to demonstrate a significant effect on survival in HCC. With the approval of sorafenib being given the significance of a milestone, systemic treatment of HCC is no longer regarded as ineffective [50].

34. ***Honary et al.,*** **(2007)** has studied the effect of film coating solution containing different grades of HPMC (E5, E15 and E50) with and without polyethylene glycol (with various molecular weights), for the characterization of pharmaceutical products [51].

35. ***Flaherty et al.,*** **(2007)** reported that **s**orafenib is an orally available inhibitor of vascular endothelial growth factor receptors, platelet-derived growth factor receptor-β, and RAF kinases. A dose of 400 mg twice daily administered continuously was selected for phase 2 testing, although 600 mg twice daily formally met criteria for a maximum tolerated dose. A phase 3 trial with sorafenib confirmed a benefit of therapy across the vast majority of patients treated with sorafenib as opposed to placebo [52].

36. ***Gloria Gamat et al.,*** **(2007)** reported the large scale multinational trial, conducted by researchers from the Mount Sinai School of Medicine in New York and Hospital Clinic of Barcelona (Spain), sorafenib pill was found to work on tumors within the liver and those that have already spread in other parts of the body [53].

37. ***Kane Rc et al.,*** **(2006).** This report describes the U.S. Food and Drug Administration (FDA) review and approval of sorafenib (Nexavar, BAY43-9006), a new small-molecule, oral, multi-kinase inhibitor for the treatment of patients with advanced renal cell carcinoma (RCC). The recommended dose is 400 mg (two 200-mg tablets) twice daily taken either 1 h before or 2 h after meals. Adverse events were accommodated by temporary dose interruptions or reductions [54].

38. ***Care Hughes et al.,*** **(2006)** summarized the pharmacology, development, and clinical application of sorafenib, a specific tyrosine kinase and vascular growth factor inhibitor, for the treatment of renal cell carcinoma. Sorafenib is a novel oral tyrosine kinase inhibitor effective in the treatment of RCC [55].

39. ***Preetha.,*** **(2000)** has studied the effect of mode of incorporation of super disintegrants such as crosarmellose sodium, Sodium starch glycolate and crospovidone on dissolution.The results indicated that the formulation containing Croscarmellose sodium has shown best release profile than the other super disintegrants due to the rapid swelling action of the polymer [56].

40. ***Tang*** **(2000)** has studied the effect of film coating on the release of chloramphenicol maleate tablets and was observed that film coating of aqueous solution of hydroxy propyl methyl celluolose improves the dissolution profile. It was found that the increased dissolution rate is due to the easy penetration of solvent in to the HPMC, which helps in wetting of core tablet [57].

The aim of present work is to develop a pharmaceutically stable, effective and quality improved formulation containing Sorafenib tosylate as an active moiety.

To achieve this formulation, various prototype formulation trials were taken and evaluated with respect to various quality control such as dissolution. The formula will be finalized by comparing the invitro dissolution profile with the reference product.

Formulation of potent drug molecules as a dosage form still draws continuous interest and challenges against optimization towards pharmacokinetic parameters like absorption, onset of action, bio-availability and also economic factors. Sorafenib tosylate, antineoplastic agent, is a multikinase inhibitor used to treat Renal Cell Carcinoma (RCC). RCC is a form of kidney cancer which accounts for 90-95% of tumours arising from the kidney and represents approximately 2% of all adult malignant tumours. Treatment of RCC with sorafenib tosylate increases the overall surveillance of the patient up to 40%.

The main objective of the present study is to:

1. To formulate and evaluate Sorafenib tosylate film coated tablets.

2. Improve the Bioavailability of the drug: Sorafenib tosylate bioavailability is 29-49%. By the use of disintegrants, the bioavailability of the drug can be enhanced.

3. To determine the best fit dissolution profile for the dosage form.

4. To study the release profile of the dosage form and to compare their drug release profile with the reference product.

5. To provide a low cost generic version of the reference product (Nexavar).

The present proposed research work was planned as per the following experimental protocol

- **Literature survey:**

Literature survey on the various works carried out on this topic is reviewed.

- **Procurement of chemicals:**

Procurement of drug and other ingredients required for the study.

- **Preformulation:**

  a. Physical observation

  b. Bulk density

  c. Tapped density

  d. Hausner‘s Ratio

  e. Car‘s index

  f. Particle size distribution

  g. Solubility

  h. Compatibility studies of drug with various excipients

- **Formulation:**

  Tablets will be prepared by compression method using various grades of excipients in different ratios.

- **Film coating tablets:**

  Film coating will be done to prepare tablets by using film coating polymer like HPMC, Advantia Prime Pink.

- **Evaluation of tablets:**

  Tablet appearance

  Thickness

  Hardness

  Disintegration test

  % Friability

  Weight variation

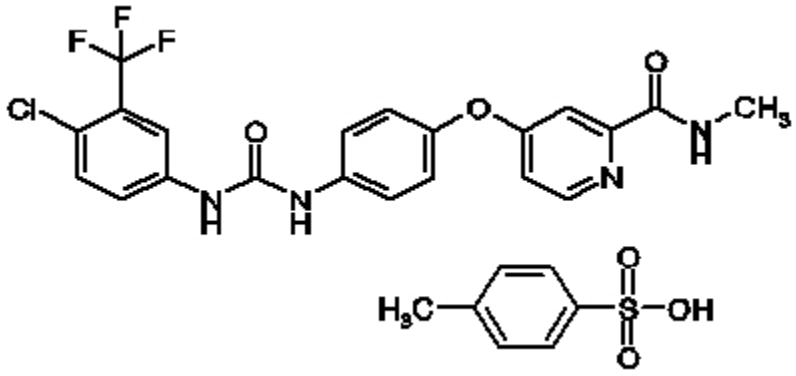
  Content uniformity

  in vitro dissolution testing.

Drug profile

Sorafenib tosylate [58] is an orally active, antineoplastic agent which acts as a protein kinase inhibitor.

Structural formula:



CAS number **:** 284461-73-0

Molecular formula **:** $C_{21}H_{16}ClF_3N_4O_3$

Molecular Weight **:** 464.825

IUPAC name **:** 4-[4-[[4-chloro-3-(trifluoromethyl)phenyl]carbamoylamino] phenoxy]-*N*-methyl-pyridine-2-carboxamide

Description **:** White to pale yellow in colour

Solubility **:** Soluble in PEG

Slightly soluble in ethanol

Insoluble in water

Category **:** Multikinase inhibitor

Melting Point **:** 187.6

Taste & Odour **:** Tasteless, Odourless

Absorption **:** Absorbed through GI tract

Protein binding **:** 99.5%

Half life **:** 25- 48 hrs

Clearance **:** 1280 ±67 mL/min.

logP **:** 4.12 and 4.34

pKa **:**13.99

Dose **:** 200 mg daily in divided doses

C_{max} **:** 12.5 μmol/L

T_{max} **:** 4 hrs

Bioavailability **:** 25- 49%

Clinical pharmacology:

Mechanism of action: Sorafenib is a protein kinase inhibitor that decreases tumour cell proliferation. It has shown to inhibit multiple intracellular (CRAF,BRAF) and cell surface kinases like KIT, FLT, RET, VEGFR, PDGFR. Several of these kinases are involved in tumour cell signaling, angiogenesis and apoptosis. Sorafenib inhibit tumour growth and angiogenesis of human renal cell carcinoma [59].

Pharmacokinetics:

Absorption:

Following oral administration, sorafenib reaches peak plasma levels in approximately 3 hours. When given with a moderate-fat meal (30% fat; 700 calories), bioavailability was similar to that in the fasted state. With a high-fat meal (50% fat; 900 calories), sorafenib bioavailability was reduced by 29% compared to administration in the fasted state. It is recommended that be sorafenib administered without food. Mean C_{max} and AUC increased less than proportionally beyond doses of 400 mg administered orally twice daily.

Distribution: *In vitro* binding of sorafenib to human plasma proteins is 99.5%. Human serum albumin, α-globulin and the low density lipoprotein are the main binding proteins. Sorafenib was equally distributed between plasma and blood cells. The binding of sorafenib to the plasma is pH dependent. The fraction unbound decreased to 0.165% at pH7.99 and increased to 1.80% at acidic pH 6.78.

Metabolism: Sorafenib is metabolized primarily in the liver, undergoing oxidative metabolism, mediated by CYP3A4, as well as glucuronidation mediated by UGT1A9. Sorafenib accounts for approximately 70-85% of the circulating analytes in plasma at steady-state. Eight metabolites of sorafenib have been identified, of which five have been detected in plasma. The main circulating metabolite of sorafenib in plasma, the pyridine *N* -oxide, shows *in vitro* potency similar to that of sorafenib. This metabolite comprises approximately 9-16% of circulating analytes at steady-state.

Excretion: Following oral administration of a 100 mg dose of a solution of Sorafenib, 96% of the dose was recovered within 14 days, with 77% of the dose excreted in feces, and 19% of the dose excreted in urine as glucuronidated metabolites. Unchanged sorafenib, accounting for 51% of the dose, was found in feces but not in urine.

Drug interactions: Sorafenib tosylate has found to have drug interactions with carboplatin, paclitaxel, docetaxel, doxorubicin, fluorouracil and neomycin.

Dosing and administration: 400 mg (2 tablets) orally twice daily without food. Treatment interruption and/or dose reduction may be needed to manage suspected adverse drug reactions. Dose may be reduced to 400 mg once daily or to 400 mg every other day.

Excipient Profile

MICROCYSTALLINE CELLULOSE [60]

Nonproprietary Names:

BP: Microcrystalline cellulose

IP: Microcrystalline cellulose

PhEur: Cellulosum microcristallinum

USPNF: Microcrystalline cellulose

Synonyms:

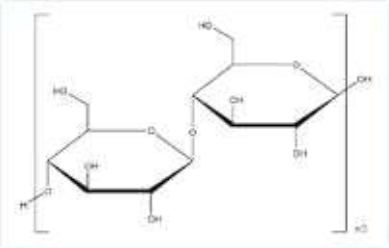
Avicel PH, Celex, cellulose gel, Celphere, Ceolus KG, crystalline cellulose, E460, Emcocel, Ethispheres, *Fibrocel,* Pharmacel, *Tabulose,* Vivapur.

Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Empirical Formula and Molecular Weight: $(C_6H_{10}O_5)_n$ ≈36 000 where $n \approx 220$.

Molecular structure:



Functional Category:

Adsorbent; Suspending agent; as a Diluent in tablets and capsules; tablet disintegrant.

Applications in Pharmaceutical Formulation or Technology:

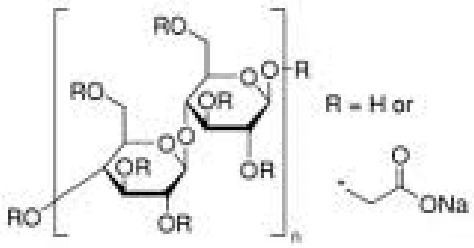
Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression processes. In addition to its use as a binder/diluent, microcrystalline cellulose also has some lubricant and disintegrates properties that make it useful in tableting. Microcrystalline cellulose is also used in cosmetics and food products [61,62]. Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

CROSCARMELLOSE SODIUM [63,64]

Nonproprietary Name: Croscarmellose sodium

Synonyms: Ac-di-sol; carmellosum natricum conexum; Crosslinked carboxymethylcellulose sodium; Explocel:modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol.

Chemical Name: Cellulose, carboxy methyl ether, sodium salt.



Functional Category: Tablet and capsule disintegrant.

Description: Croscarmellose sodium occurs as an odorless, white or grayish-white powder.

Solubility: Insoluble in water, although Croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. It is practically insoluble in acetone, ethanol and toluene.

Stability and Storage Conditions: Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with croscarmellose sodium as a disintegrant showed no significant difference in drug dissolution after storage at 300^0C for 14 months. Croscarmellose sodium should be stored in a well closed container in a cool, dry place.

Incompatibilities: The efficacy of Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct compression process that contain hygroscopic excipients such as sorbitol. Croscarmellose Sodium is not compatible with strong acids or with soluble salts of iron and metals such as aluminum, mercury and zinc.

Applications: Croscarmellose sodium is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets and granules. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. When used in wet granulations, the croscarmellose sodium should be added in both the wet and dry stages of the process (intra and extra- granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3%w/w in tablet prepared by wet granulation process.

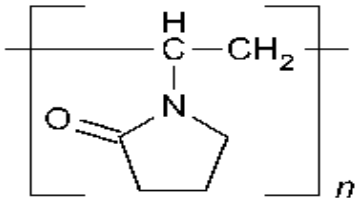
Related Substances: Carboxy methyl cellulose calcium: Carboxy methyl cellulose sodium.

CROSPOVIDONE [65]

Nonproprietary Name: Crospovidone.

Synonyms: Crospovidonum; Polyplasdone XL; Polyvinylpolypyrrolidone.

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer



Empirical Formula: (C_6H_9NO) n

Molecular Weight: >1 000 000

Functional Category: Tablet disintegrant

Description: Crospovidone is a white to creamy-white, finely divided, free flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility: Practically insoluble in water and most common organic solvents.

Stability and Storage Conditions: Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities: Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials.

Applications: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2-5 % concentration in tablets prepared by direct compression or wet- and dry-granulation methods. It can also be used as a solubility enhancer.

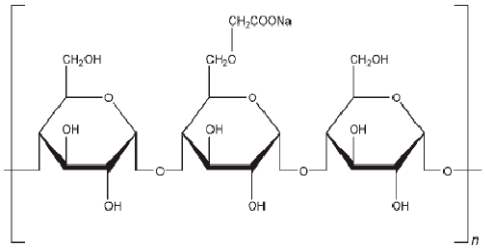
Related Substances: povidone.

SODIUM STARCH GLYCOLATE [66]

Nonproprietary Name:

Synonyms: Carboxymethyl starch, sodium salt; carboxymethylamylumnatricum; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P

Chemical Name: Sodium carboxymethyl starch.



Functional Category: Tablet and capsule disintegrant.

Description: It is a white or almost white free-flowing very hygroscopic powder. The PhEur 6.0 states that when examined under a microscope it is seen to consist of: granules irregularly shaped, ovoid or pear-shaped, 30–100 mm in size, or rounded,10–35 mm in size; compound granules consisting of 2–4 components occur occasionally; the granules have an eccentric hilum and clearly visible concentric striations. The granules show considerable swelling in contact with water [67,68].

Solubility: Practically insoluble in water and insoluble in most organic solvents.

Stability and Storage Conditions: Tablets prepared with sodium starch glycolate have good storage properties. Sodium starch glycolate is stable although very hygroscopic, and should be

stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking. The physical properties of sodium starch glycolate remain changed for up to 3 years if it is stored at moderate temperatures and humidity.

Incompatibilities: Sodium starch glycolate is incompatible with ascorbic acid.

Applications: It is widely used in oral pharmaceuticals as a disintegrant in tablets and capsule formulations. It is recommended to use in tablets prepared by either direct-compression or wet granulation processes [69].

HYDROXYPROPYL METHYL CELLULOSE (HPMC) [70]

Non-proprietary names:

IP: Hydroxypropylmethylcellulose

BP: Hypromellose

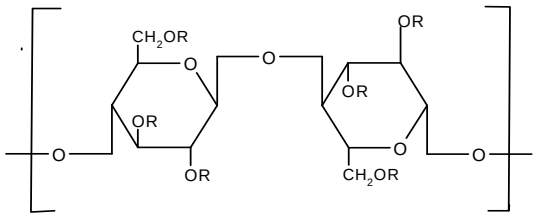
Ph Eur: Methylhydroxypropylcellulosum

USP: Hypromellose

Chemical Name: Cellulose, 2-hydroxypropyl methyl ether

Synonyms: Methyl Hydroxy Propyl cellulose; Propylene Glycol ether of methylcellulose; CulminalHPMC.

Structural Formula:



Where R is H, CH_3 or CH_3-CH(OH)-CH_2

Physical and chemical properties

Molecular weight : 10,000 - 15,00,000

Color : White to creamy-white

Nature : Fibrous or granular powder

Odor : Odorless

Taste : Tasteless

Density : 0.3-1.3 g/mL

Specific gravity : 1.26

Solubility : Soluble in cold water, practically insoluble in chloroform, ethanol (95%) and ether but soluble in mixture of ethanol and dichloromethane.

Viscosity : HPMC-K4M-3,000-5600mPas

K15M: 12,000-21,000mPas

K100M: 80,000-1, 20,000mPas

Melting point : Browns at 190-200 °C, chars at 225-230 °C, glass transition temperature is 170-180°C.

Functional Category:

Used as Coating agent, film-forming, rate-controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity-increasing agent.

Applications:

HPMC is widely used in oral and topical pharmaceutical formulation. In oral products HPMC is primarily used as tablet binder. Concentration between 2-5% w/w may be used as a binder in either wet or dry granulation process. Concentration of 0.45-1% w/w may be added as a thickening agent to vehicle for eye drops and artificial tear solution. HPMC is used as an adhesive in plastic bandage and as a wetting agent for hard contact lenses. It is widely used in cosmetics and food products. In addition, HPMC is used as an emulsifier, suspending agent and

stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particle from coalescing or agglomerating thus, inhibiting the formation of sediments [71].

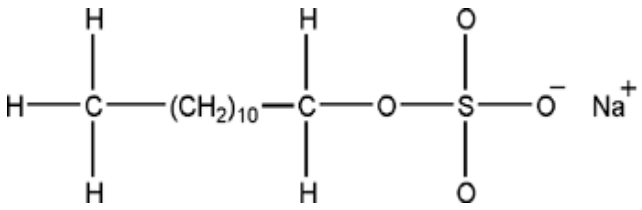
Stability and storage

It is stable although it is slightly hygroscopic. The bulk material should be stored in an airtight container in a cool and dry place. Increased in temperature reduces the viscosity of the solution.

Safety: It is generally regarded as a non-toxic and non-irritant material, so it is widely used in many oral and topical pharmaceutical formulations. Excessive consumption of HPMC may have laxative effect.

SODIUM LAURYL SULPHATE [72]

Synonyms: Dodecyl sodium sulphate; Elfan 240



Empirical Formula: $C_{12}H_{25}NaO_4S$

Molecular Weight: 288.37

Solubility: Freely soluble in water forming opalescent solution, practically insoluble in chloroform, ether.

Functional Category: Anionic surfactant.

Description: White cream to pale yellow coloured crystals, bitter in taste.

Incompatibilities: Incompatible with strong oxidizing agents.

Applications: SDS is mainly used in detergents for laundry and many cleaning applications. SDS is a highly effective surfactant and is used in any task requiring the removal of oily stains and residues.

MAGNESIUM STEARATE [73,74]

Nonproprietary Names:

BP: Magnesium stearate

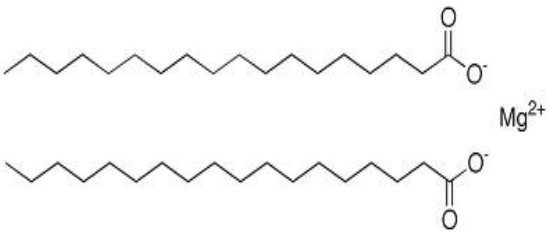
IP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

Synonyms: Magnesium octadecanoate; octadecanoic acid; magnesium salt; stearic acid.

Chemical Name : Octadecanoic acid magnesium salt



Functional Category : Tablet and capsule lubricant.

Description:

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility:

Practically insoluble in ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Chemicals and Equipments used

Table 2: List of materials used

S.No	Materials	Manufacturer	Supplier
1	Sorfenib	Natco Pharma Ltd., Hyderabad	Natco Pharma Ltd., Hyderabad
2	Microcrystalline cellulose	FMC Bio Polymer, New York	Signet Chemical Corporation, Mumbai
3	Croscarmellose	FMC Bio Polymer, Ireland	Signet Chemical Corporation, Mumbai
4	Hypromellose	Evonikdegussa Antwerpen	Kancham Agencies, Tamil nadu
5	Crospovidone	ISP Technologies USA	Anshul Agencies, Mumbai
6	Magnesium stearate	Luzenac Valchisone, Italy	Signet Chemical Corporation, Mumbai
7	Advantia Prime Pink	Ferro Industriasquimicas, Portugal	Signet Chemical Corporation, Mumbai
8	Sodium starch glycolate	DMV Fonterra Excipients	Kamarlal & Co, Hyderabad
9	Sodium lauryl sulphate	Ferro Corporations, USA	Signet Chemical Corporation, Mumbai
10	Purified water	Natco Pharma Limited	Natco Pharma Limited

Table 3: List of equipments used:

S.no	Equipment	Company
1	Electronic balance	Metler Toledo, Mumbai
2	Bulk density apparatus	Electrolab, Mumbai
3	Rapid mixer granulator	Anchor, Mumbai
4	Double cone blender	Erweka
5	Rotary Tablet punching machine	Rimek, Mumbai
6	Friability test apparatus	Electrolab, Mumbai
7	Tablet hardness tester	Schleuniger hardness tester
8	Disintegration test apparatus	Electrolab , Mumbai
9	Tablet dissolution apparatus	Electrolab , Mumbai
10	HPLC	WATERS
11	Pharma R&D coater	Electrolab , Mumbai
12	Stability chamber	Thermolab

Preformulation studies: [75]

Preformulation studies are performed to investigate the physical and chemical properties of a drug substance alone and also when combined with other substances such as excipients. It is the first step in the rational development of dosage forms.

Objective: The overall objective of performing pre-formulation testing is to generate information that will be helpful in developing a stable and bioavailable dosage form when combined with excipients.

Scope: The use of pre-formulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product and at same time provides the basis for optimization of the drug -product quality.

Organoleptic properties: The color, odour and taste of the drug were recorded using descriptive terminology.

Angle of Repose: The flow property was determined by measuring the angle of repose. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose= $\tan^{-1}$ (h/r)

Where h = height and r = radius

Procedure:

20 gms of the sample was taken and passed through the funnel slowly, to form a heap. The height of the powder heap formed was measured and the circumference formed was drawn with a pencil on the graph paper. The radius was measured and the angle of repose was determined. This was repeated three times for a sample.

Bulk density:

Bulk density is ratio of given mass of powder and its bulk volume. Bulk density was determined by measuring the volume of known mass of powder sample that has been passed through the screen in to graduated cylinder.

Bulk density = M / V_0

Where M= mass of the powder; V_0=bulk volume of the powder.

Limits:

It has been stated that the bulk density values having less than 1.2 g/cm^3 indicates good packing and values greater than 1.5 g/cm^3 indicates poor packing.

Tapped density: [75]

Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 10 g of pure drug was filled in 100 mL graduated cylinder of tap density tester. The mechanical tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for additional 750 times and volume was noted. The difference between two tapping volumes was calculated.

Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until differences between volumes of subsequent tapping was less than 2%. This volume was noted as the final tapped volume (Vo). The tapped density (Dt) was calculated in g/mL by the formula:

$$\text{Tap density} = M / Vo$$

Where M = mass of the powder, Vo = final tapping volume of the powder.

Compressibility index and Hausner ratio: [76]

In the recent years, the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics.

The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials, because all of these can influence the observed compressibility index. The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and tapped volume of a powder.

Basic methods for the determination of compressibility index and Hausner ratio:

While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume (V_O), and the final tapped volume, (V_f), of the powder after tapping the material until no further volume changes occur.

The compressibility index and the Hausner ratio is calculated as follows:

Compressibility index = $100 \times V_0\text{-}V_f/V_0$

Hausner ratio = V_0/V_f

Where, V_0 = apparent volume, V_f = final tapped volume.

Alternatively, the compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner ratio = tapped density / bulk density

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner ratio, the generally accepted scale of flow ability is described in the following table.

Flow properties and corresponding Angle of repose, Compressibility index and Hausner ratio.

Table 4: Flow properties determination

S. No	Flow properties	Angle of repose(θ)	Compressibility Index (%)	Hausner ratio
1	Excellent	25-30	<10	1.00-1.11
2	Good	31-35	11-15	1.12-1.18
3	Fair	36-40	16-20	1.19-1.25
4	Passable	41-45	21-25	1.26-1.34
5	Poor	46-55	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.59
7	Very very poor	> 66	>38	>1.6

Drug-Excipient compatibility studies:

Drug is in intimate contact with one or more excipients in all the dosage forms. Later it could affect the stability of drug. Knowledge of drug-excipients interaction is useful in selecting an appropriate excipient.

Procedure:

API and excipient are taken in the ratios mentioned elsewhere and mixed together in a polybag for 5 min. Each mixture is allotted with a sample code for identification. 4 sets of sample were allocated where each sample mixture is divided into 1g and transferred to its corresponding glass vial (USP Type I) at different conditions.

All vials are properly sealed and loaded at respective conditions. The samples checked for their description, related substance and water content by KF. The prepared drug and excipient mixtures were evaluated at various intervals for related substances by HPLC as per the following conditions and time intervals as per the procedure mentioned below**.**

Table 5: Sampling Schedule:

S.No	Condition	Duration	No. of Sets
1	Initial	0 days	1
2	$55^0C \pm 2^0C$	14 days	1
3	40 ± 2^0C & 75 ± 5% RH	14 days	1
4	40 ± 2^0C & 75 ± 5% RH	28 days	1

Then they are subjected for analysis of description, assay, loss on drying and purity.

Solubility studies:

Solubility was determined by adding the solute in small incremental amount to fixed volume of the solvents. After each addition, the system was vigorously shaken and examined visually for any undissolved solute particles. Solubility of acid or base drug is pH dependent. It is determined over the pH range 1-8.

Water Content:

35 mL of a mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric end point, to consume any moisture that may be present (disregard the volume consumed, since it does not enter into the calculation). Accurately 350 mg of the drug was weighed and transferred in to the titration vessel, mixed and titrated with the KF reagent to the electrometric endpoint. The water content of the specimen in mg taken by the formulae:

Calculation:

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where,

S = Volume in ml of reagent consumed in the second titration

F = Water equivalent factor of KF reagent

W = Weight of sample taken in mg

Loss on drying (LOD):

The Loss on drying test is designed to measure the amount of water and volatile matters in a sample when the sample is dried under specified conditions. The loss on drying of the blend (2 g) was determined by using electronic LOD apparatus at 105°C.

EVALUATION OF TABLETS: [77]

The quantitative evaluation and assessment of a tablets chemical, physical and bioavailability properties are important in the design of tablets to monitor product

quality. There are various standards that have been set in the various pharmacopoeias regarding the quality of pharmaceutical tablets. These include the diameter, size, shape, thickness, weight, hardness, disintegration and dissolution characters

1. Physical Appearance:

The general appearance of a tablet, its identity and general elegance is essential for consumer acceptance, for control of lot-to-lot uniformity and tablet-to-tablet uniformity. The control of general appearance involves the measurement of size, shape, colour, presence or absence of odour, taste etc.

2. Size & Shape:

It was dimensionally described & controlled. The thickness of a tablet is only variables. Tablet thickness was measured by micro-meter. Tablet thickness should be controlled within a limit of ± 5% variation of standard value.

3. Weight variation test:

This is an in process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets. Different pharmacopoeias specify different limits for these weight variation tests. These tests are primarily based on the comparison of the weight of the individual tablets of a sample of tablets with an upper and lower percentage limit of the observed sample average. The USP has provided limits for the average weight of uncoated compressed tablets. These are applicable when the tablet contains 50mg or more of the drug substance or when the later comprises 50% or more, by weight of the dosage form.

Method:

Twenty tablets were weighed individually and the average weight was calculated. The individual tablet weights are then compared to the average weight. As per USP not more than two tablets should differ in their average weight by more than percentages stated and no tablet must differ by more than double the relevant percentage.

Table 6: Limits for tablet weight variation test:

Average weight of tablet (mg)	% Difference allowed
130 or less	10 %
From 130 to 324	7.5 %
> 324	5 %

4. Content Uniformity:

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch.

Method:

Randomly 30 tablets were selected and 10 of these were assayed individually. According to the quality standards the tablet pass the test if 9 of the 10 tablets must contain not less than 85% and not more than 115% of the labeled drug content and the 10th tablet may not contain less than 75% and more than 125% of the labeled content. If these conditions are not met, remaining 20 tablets were assayed individually and none may fall outside of the 85 to 115% range.

ASSAY OF SORAFENIB [78]

The sorafenib content in each tablet was assayed by HPLC method using X-Terra RP-18 column- (100 x 4.6 mm, 5 µm) by injecting 20 µL of sample with a flow rate of 2.0 mL/ minute and a run time of 15 minutes at an ambient temperature using a UV detector at 293 nm.

Preparations:

Buffer preparation:

2.72 g of potassium di hydrogen orthophosphate was weighed accurately and transferred in to 1000 mL standard flask and the volume made with distilled water. pH was made to 3.0 with orthophosphoric acid.

Mobile phase preparation:

Phosphate Buffer, Acetonitrile and Tetrahydrofuran in the ratio of 530:395:75 v/v was prepared and filtered through 0.22 µm membrane filter and degassed.

Diluent preparation:

Methanol and Acetonitrile in the ratio of 50:50 v/v was prepared and filtered in a membrane filter and degassed.

26.2 mg of sorafenib tosylate was weighed and transferred to 100 mL of volumetric flask added with 60 mL of dissolution medium and sonicated to dissolve. The solution was cooled to room and 5.0 mL of the standard stock preparation transferred to a 100 mL volumetric flask and volume made with dissolution medium [79].

Sample preparation:

20 tablets of sorafenib were taken and powdered. From this powder equivalent to 200 mg of Sorafenib was transferred into a 250 mL volumetric flask and added with 160 mL of dissolution medium. The resulting mixture was shaken for 15 minutes on orbital shaker and sonicated for 30 minutes with occasional shaking. The mixture was cooled to room temperature and the volume was made with dissolution medium and filtered through 0.22 µm membrane filter. From the above solution 3.0 mL was taken and made to 250 mL in a volumetric flask using dilution medium [80].

System suitability:

Chromatograph the standard preparation (Six replicate injections), measure the peak area responses for the analyte peak and evaluate the system suitability parameters as directed.

Acceptance criteria:

% RSD for replicate injections of peak area response of the sorafenib peak from the standard preparation should be not more than 2.0

The Tailing factor for sorafenib peak should be not more than 2.0

The number of theoretical plates for sorafenib peak should be not less than 2000.

Procedure:

20 µL of the diluent as blank, standard preparation and sample preparation were injected separately into the chromatograph and peak area responses for the analyte were recorded and measured. Content of sorafenib(%) in the portion of sorafenib tablets was calculated by the formula.

5. Thickness and diameter: The thickness and diameter of 10 tablets were recorded during the process of compression using vernier calipers.

6. Hardness:

Hardness, more appropriately called crushing strength is used to determine the need for pressure adjustment on tablet machine. If the tablet is too hard, it may not disintegrate in the required period of time to meet the dissolution specifications; if it is too soft, it may not be able to withstand the handling during subsequent processing such as coating or packaging and shipping operations [81]. The force required to break the tablet is measured in kilograms. The small and portable hardness tester measures the force required to break the tablet when the force generated by a coil spring is applied diametrically to the tablet.

7. Friability:

Friction and shock are the forces that most often cause tablets to chip, cap or break. The friability test is closely related to tablet hardness and designed to evaluate the ability of the tablet to withstand abrasion in packaging, handling and shipping. It is usually measured by the use of the Roche friabilator.

Method:

20 tablets were weighed and placed in the apparatus where they are exposed to rolling and repeated shocks as they fall 6 inches in each turn within the apparatus. After four minutes of this treatment or 100 revolutions, the tablets are weighed and the weight compared with the initial weight. The loss due to abrasion is a measure of the tablet friability. The value is expressed as a percentage. A maximum weight loss of not more than 1% of the weight of the tablets being tested during the friability test is considered generally acceptable and any broken or smashed tablets are not picked.

The percentage friability was determined by the formula:

% Friability = $(W_1-W_2) / W_1 X 100$

W_1 = Weight of tablets before test

W_2 = Weight of tablets after test

8. Disintegration test:

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen. Generally, the test is useful as a quality assurance tool for conventional dosage forms [82].

Method:

The U.S.P. device to test disintegration uses 6 glass tubes that are open at the top and 10 mesh screen at the bottom end. To test for disintegration time, one tablet is placed in each tube and the basket rack is positioned in a 1-L beaker of water, simulated gastric fluid or simulated intestinal fluid at 37 ± 2° C such that the tablet remain 2.5 cm below the surface of liquid on their upward movement and not closer than 2.5 cm from the bottom of the beaker in their downward movement. The basket containing the tablets was moved up and down through a distance of 5-6 cm at a frequency of 28 to 32 cycles per minute. Floating of the tablets can be prevented by placing perforated plastic discs on each tablet. According to the test the tablet must disintegrate and all particles must pass through the 10 mesh screen in the time specified. If any residue remains, it must have a soft mass. If one or two tablets fail to disintegrate, the test is repeated using 12 tablets.

Disintegration time: Uncoated tablet: not more than15 minutes

Coated tablet: not more than 30 minutes

9. Dissolution:

Dissolution is the process by which a solid solute enters a solution [83]. In the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability [84].

Evaluation of dissolution profile of sorafenib tablet :

The dissolution test was carried out for the prepared tablets was carried out in USP type-2 (Paddle) apparatus using 900 mL of 0.1M Hydrochloric acid with 1% SDS as medium at a temperature of 37 ºC ± 0.5 ˚C with a paddle speed of 75 rpm. Samples were withdrawn at 5, 10, 15, 20 and 30 minutes time interval for the content evaluation.

Preparation of Dissolution medium (0.1M Hydrochloric acid with 1% SDS):

8.5 mL of hydrochloric acid was pipetted out to a standard flask and volume made to 1000 mL with distilled water

Chromatographic conditions:

Column- X-Terra RP- 18 (100 x 4.6 mm), 5 µm

Flow rate – 2.0 mL/ minute

Wavelength- UV-293 nm

Column temperature- Ambient

Injection volume- 10 µL

Run time- 15 minutes

Preparations:

Buffer preparation: Accurately 2.72 g of Potassium dihydrogen orthophosphate was weighed and transferred into 1000 mL of purified water and mixed well. The solution pH was adjusted to 3.0 with dilute orthophosphoric acid.

Mobile phase preparation: Mixture of Buffer, Acetonitrile and Tetrahydrofuran in the ratio of 530:395:75 V/V were prepared and was filtered through 0.22 µm membrane filter and degassed.

Standard preparation:

About 26.2 mg of sorafenib tosylate was accurately weighed and transferred into 100 mL volumetric flask and added with 60 mL of dissolution medium and sonicated to dissolve. The solution was cooled to room temperature and diluted to volume with dissolution medium. 5.0 mL of the standard stock preparation was transferred into a 100 mL volumetric flask and dilute to volume with dissolution medium.

Sample preparation:

One tablet of sorafenib was kept in each of six dissolution flasks containing 900 mL of dissolution medium, previously maintained at 37ºC, taking care to exclude air bubbles from the surface of each dosage unit and immediately operate the apparatus for specified time intervals. After completion of each specified time interval, 2 mL portion of solution from zone midway between the surface of the dissolution medium and top of the rotating blade, not less than 1cm from vessel wall and filtered through 0.22 µm membrane filter.

2.0 mL of the above solution was transferred into a 20 mL volumetric flask and volume diluted to mark with dissolution medium.

System suitability:

The chromatogram for the standard preparation (Six replicate injections), the peak area responses measured for the analyte peak and evaluated the system suitability parameters as directed.

Acceptance criteria:

% RSD for replicate injections of peak area response of sorafenib peak from the standard preparation should not be more than 2.0.

The Tailing factor for sorafenib peak should be not more than 2.0.

The number of theoretical plates for sorafenib peak should be not less than 2000.

Procedure:

10 µL of the dissolution medium as blank, standard preparation and sample preparation were injected separately into chromatograph and chromatograms were recorded for peak area responses. The % of drug content (sorafenib) in the portion of sorafenib tablets was then calculated

Related Impurities:

Chromatographic conditions:

The level of related impurities were assayed by HPLC using X-Terra RP- 18 column- (100 x 4.6 mm, 5 µm) by injecting 10 µL of sample with a flow rate of 0.8 mL/ minute and a run time of 45 minutes at 30°C using a UV detector at 265 nm and 293 nm.

Preparations:

Buffer preparation:

2.72 g 0f Potassium Dihydrogen Orthophosphate was weighed and transferred into 1000 mL of purified water and mixed well. The solution pH was adjusted to 3.0 with dilute orthophosphoric acid**.**

Mobile phase-A preparation:

Buffer preparation was used as mobile phase-A. it was filtered through 0.22 µm membrane filter and degassed.

Mobile phase-B preparation:

Mixture of Acetonitrile and Tetrahydrofuran in the ratio of 90:10 v/v was prepared and the solution was filtered through 0.22 µm membrane filter and degassed.

Diluent preparation:

Prepare a filtered and degassed mixture of Methanol and Acetonitrile in the ratio of 50:50 v/v respectively.

Placebo preparation:

Placebo powder equivalent to 100 mg of sorafenib was weighed accurately and transferred into a 200 mL volumetric flask and added with 160 mL of dilution medium and sonicated for 20 minutes with occasional shaking. The solution was cooled to room temperature and the volume was made and filtered through 0.22 µm membrane filter and degassed.

Peak Identification solution preparation:

About each 5.0 mg of Impurity-A, impurity-B, Impurity-C was accurately weighed and transferred into a 50 mL volumetric flask, added with 30 mL of dilution medium and sonicated to dissolve. The solution was cooled and the volume was made.

137.0 mg of sorafenib tosylate working standard (equivalent to 100 mg of sorafenib) was weighed and transferred into a 200 mL volumetric flask. 160 mL of dilution medium was added and sonicated for 20 min with occasional shaking. The resulting solution was cooled to room temperature, added with 2.0 mL of Peak Identification solution and volume dilute to mark with diluents medium.

Standard preparation:

14 mg of sorafenib tosylate working standard was accurately weighed and transferred into a 200 mL volumetric flask, added with 160 mL of dilution medium and sonicated to dissolve. Solution was cooled to room temperature and volume was made to the mark with dilution medium.

1 mL of the above solution was transferred into a 100 mL volumetric flask and volume made with dilution medium.

Sample preparation:

20 tablets of sorafenib was powdered and powder equivalent to 100 mg of sorafenib was transferred into a 200 mL volumetric flask, added 160 mL of dilution medium, sonicated for 20 minutes with occasional shaking. The solution was cooled to room temperature volume was made and filtered through 0.22 µm PVDF filter.

System suitability:

The standard preparation (six replicate injections) and Peak Idenification solution (one injection) was chromatogramed and the peak area responses for the analyte peaks and evaluate the system suitability parameters as directed.

Acceptance criteria:

- % RSD for six replicate injections of peak area response for sorafenib peak (at 235 nm) from the standard preparation should be not more than10.0.
- %RSD for six replicate injections of peak area response for sorafenib peak (at 265 nm) from the standard preparation should be not more than 5.0.
- Tailing factor for sorafenib peak from standard preparation should not be more than 2.0.
- The number of theoretical plate count for sorafenib peak from standard preparation should not be less than 2000.
- Resolution between Impurity-C and sorafenib from peak identification solution should not be less than 1.5.

Procedure:

10 µl of diluent as blank, placebo preparation, peak identification solution preparation, blank, standard preparation and sample preparation were injected separately into the chromatograph and the chromatograms were recorded. The % of each impurity in the portion of sorafenib tablets was then calculated.

Water content (By KF Method):

Instrument: Karl Fischer titrator

35 mL of a mixture of methanol was transferred to the titration vessel and titrated with Karl Fischer reagent to the electrometric end point, to consume any moisture that may be present (disregard the volume consumed, since it does not enter into the calculation). 350 mg of the powder was accurately weighed and transferred into the titration vessel, mixed and titrated with Karl Fischer reagent to the electrometric end point. Finally the water content of the specimen in mg was calculated.

Stability studies:

The purpose of stability testing is to provide evidence of the quality of the drug substance or drug product, and how it varies with time under the influence of a variety of environmental conditions (heat, humidity, light, air etc). The final formulation was packed in suitable packing like blister and strip packs and then they will be kept at different temperature, humidity conditions and the samples will be analyzed for their physical and chemical properties.

Table 7: ICH guide lines for Stability Study

Study	Storage condition	Time period
Long term	25°C±2°C/60% RH±5% RH or 30°C±2°C/65% RH±5% RH	12 month
Intermediate	30°C±2°C/65% RH±5% RH	6 month
Accelerated	40°C±2°C/75% RH±5% RH	6 month

Experimental Investigation

Innovator product details:

Product name	**:** Nexavar
Label claim	**:** Each tablet contains 200 mg of sorafenib
Manufactured by	**:** Bayers health care
Description	**:** Red in colour, debossed with **Bayer cross** on one side and **200** on other side
Inactive ingredients	**:** Inactive ingredients of the tablets are Microcrystalline cellulose, Croscarmellose, Hydroxypropylmethylcellulose, Magnesium stearate.
Thickness	**:** 4.44 mm
Width	**:** 7.64 mm
Diameter	**:** 10.05 mm
Storage	**:** Store at 25°C (77°F);
Dissolution Apparatus	**:** Paddle type (USP apparatus II)
Dissolution Medium	**:** 0.1M Hydrochloric acid with 1% SDS

Dissolution medium Volume : 900 mL

Time points	**:** 5, 10, 15, 20, 30 minutes
Speed	**: 7**5 rpm

FORMULATION DEVELOPMENT

Procedures:

Table 8. List of excipients used in the formulation:

Purpose	Ingredients
Diluent	Microcrystalline cellulose
Binder	Hypromellose
Disintegrant	Croscarmellose
Solubility enhancer	Sodium lauryl sulphate
Lubricant	Magnesium stearate
Colourant	Advantia Prime Pink

Table 9: Composition of Sorafenib Tosylate tablets:

Ingredients	**F1 (mg)**	**F2 (mg)**	**F3* (mg)**	**F4 (mg)**	**F5 (mg)**	**F6 (mg)**	**F7 (mg)**	**F8 (mg)**	**F9 (mg)**	**F10 (mg)**	**F11 (mg)**
Sorafenib tosylate	274.0	274.0	274.0	274.0	274.0	274.0	274.0	274.0	274.0	274.0	274.0
Avicel	60.55	60.55	57.50	57.50	57.50	65.30	49.70	41.90	61.40	53.60	49.70
Croscarmellose	37.00	37.00	39.00	-	-	31.20	46.80	54.60	39.00	39.00	39.00
Crospovidone	-	-	-	39.00	-	-	-	-	-	-	-
Sodium starchglycolate	-	-	-	-	39.00	-	-	-	-	-	-
Hypromellose	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80
Sodium lauryl sulphate	7.80	7.80	7.80	7.80	7.80	7.80	7.80	7.80	3.90	11.70	15.60
Magnesium stearate	2.85	2.85	3.90	3.90	3.90	3.90	3.90	3.90	3.90	3.90	3.90
Purified water	-	-	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Advantia Prime Pink	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Total (mg)	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**	**400 mg**

*-Optimized formula

Procedure for Formulation 1: (Direct compression): [85]

API, microcrystalline cellulose PH102, croscarmellose, sodium lauryl sulphate were weighed and sifted individually through 40 # mesh. All the ingredients were transferred to poly bag and mixed for 3 minutes and the blend was passed through 40 # mesh and mixed thoroughly. Magnesium stearate used as lubricant was weighed separately, sieved through 40 # mesh and blended with the ingredients for 2 minutes. The mixture was compressed using oblong punches.

Procedure for Formulation 2: (Slugging) [85]

API, microcrystalline cellulose PH102, croscarmellose, hypromellose, sodium lauryl sulphate were weighed accurately and mixed in a polybag for 10 minutes and sifted through 40 # mesh. Weighed quantity of magnesium stearate sifted through 40 # mesh was then added to above blend and mixed for 2 min in a poly bag. Lubricated blend is slugged with 18 mm round flat punches. Slugs obtained were milled in multimill using 8mm mesh and further milled with 2mm mesh. The granules obtained were passed through 18 # mesh.

Procedure for Formulation 3 to 11: (Wet Granulation) [86]

Ingredients such as API, microcrystalline cellulose PH101were weighed and sifted individually through 40 # mesh and transferred to poly bag and mixed for 10 minutes and the blend was passed through 40 # mesh. Binder solution was prepared by dissolving hydroxypropyl methyl cellulose in sufficient quantity of purified water and added to the blend. The wet mass was passed through 12 # mesh and the granules obtained were dried at 60°C for 30 minutes. Dried granules were passed through 18 # mesh. Above prepared granules were lubricated with magnesium stearate and passed through 40 # mesh and was compressed using punches. Tablets obtained were coated using Advantia Prime Pink (coating material) for weight gain of each tablet up to 1% (where formulation1 and 2 is uncoated).

* In formulation 3, 4, 5; 39 mg of each of croscarmellose, sodium starch glycolate, crospovidone was taken as disintegrant respectively.

* In formulation 6, 7, 8 disintegrant concentrations were altered such as 8%, 12%, 14% concentration of croscarmellose was taken.

* In the formulation 9, 10, 11; sodium lauryl sulphate concentration was taken as 1%, 3% and 4% respectively.

* In formulation 12; the F3 formulation was increased to a batch size of 2000 tablets.

Procedure for Film Coating [87]

Film coating was done for the tablets to give a good appeal and to increase the elegance. The tablets were charged into the pan of coating machine (Ideal cures) and coated using Advantia Prime Pink. Adavntia Prime Pink composes of hydroxyl propyl methyl cellulose, hypromellose, polyethyleneglycol, titanium di oxide and ferric oxide red. The coating solution was prepared by dispersing Advantia Prime Pink (10%) in water and was sprayed over the tablets using 1.5 mm air nozzle with an atomizing air pressure of 3-4 atm. The pan speed was maintained at 30 rpm with an inlet and Outlet temperature maintained at 60^0C and 55^0C respectively. The coating was performed until required weight gain of 1% was obtained.

Evaluation of Preformulation parameters:

Micromeritic properties of excipients:

The results of compressibility index, angle of repose and Hausner's ratio were mentioned in the table below.

Table 10: Micromeritic properties of excipients

Ingredient	Bulk density(g/cm^3)	Tapped density(g/cm^3)	Angle of repose(ϕ)	Compresibility index (%)	Hausners ratio
Avicel pH101	1.62±0.13	1.43±0.18	30.4±0.08	12.9	1.16
Hypromellose	1.43±0.20	1.32±0.12	37.9±0.11	17.2	1.22
croscarmellose	1.02±0.27	0.87±0.23	38.4±0.09	19.1	1.26
Sodium starch glycolate	1.09±0.5	0.9±0.28	43.8±0.6	19.9	1.31
Crospovidone	1.06±0.2	0.96±0.11	36.1±0.3	18.6	1.18
Magnesium stearate	1.98±0.11	1.09±0.09	36.5±0.08	18.5	1.24
Sodiumlauryl sulphate	1.08±0.2	1.99±0.21	29.8±0.23	16	0.9

Inference:

All the excipients used in the formulation were shown the above results for micrometric evaluation parameters. Compressibility index of all the ingredients was found in between 12 to 19, indicates poor compressibility index. Angle of repose of all formulations are found to be between 30 to 38,

indicating all the excipients are possessing good flow properties and Hausner ratio of all excipients was found to be 1.0 to 1.2, which satisfies the limits of compressibility.

API (Active Pharmaceutical Ingredient) Characterization:

Table 11: Micromeritic properties of Active Pharmaceutical Ingredient:

S.No	Parameter	Results
1	Angle of repose	36.50± 0.12
2	Bulk Density	0.72±0.3 gm/ml
3	Tapped Density	0.54±0.2gm/ml
4	Compressibility Index	39.6±0.5%
5	Hausner's ratio	1.32±0.29

Inference: Based on the above pre-formulation results it was observed that the flow was poor and wet granulation method was suitable.

EVALUATION OF GRANULES

Table 12: Evaluation of different parameter for the trial formulation

S.No	Formulations	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner's Ratio
1	F-1	0.519	0.732	29.09	1.443
2	F-2	0.436	0.500	12.8	1.14
3	**F-3**	**0.445**	**0.505**	**11.8**	**1.13**
4	F-4	0.408	0.480	13.74	1.15
5	F-5	0.416	0.485	14.2	1.16
6	F-6	0.393	0.460	14.5	1.17
7	F-7	0.428	0.490	12.6	1.14
8	F-8	0.415	0.476	12.8	1.14
9	F-9	0.428	0.496	13.7	1.15
10	F-10	0.400	0.470	14.8	1.17
11	F-11	0.417	0.482	13.4	1.15

Solubility Profile:

Table 13: Solubility data of Sorafenib tosylate:

S. No.	Buffers	Solubility (mg/ml)
1	Water	171
2	0.1N HCl	634
3	PEG	260
4	Phosphate Buffer pH 6.8	180

Inference:

The above values of concentrations indicate the solubility of Sorafenib tosylate in different solvents. It was observed that the solubility of sorafenib in water is very low and in acidic media it shows better solubility profile

Drug-excipient compatibility studies:

Compatibility studies were conducted for drug and excipients in separate as well as in combination with different proportions at different temperature conditions for a period of two weeks and for four weeks. Here the external appearance of tablets was considered as the criteria i.e. color. After four weeks of studies all the combinations which are undergone for testing evaluated for appearance. And all the formulations showed no change in color during studies.

Results of Drug-excipient compatibility studies:

Table 14: Descriptions of drug excipients

S.No	Ingredients	Quantity (mg)	Description		
			Initial	**55°C (2weeks)**	**40±2°C /75±5 % RH (4weeks)**
1	API	1	Off white	No change	No change
2	Avicel	1	Off white	No change	No change
3	Croscarmellose	1	White	No change	No change
4	Hypromellose	1	White	No change	No change
5	SLS	1	white	No change	No change
6	Magnesium stearate	1	White	No change	No change
7	Advantia Prime Pink	1	Brick Red	No change	No change
8	API+Avicel	5:1	Off White	No Change	No Change
9	API+Hypromellose	5:1	Off white	No change	No change
10	API+Croscarmellose	5:1	Off white	No change	No change
11	API+ SLS	5:1	Off white	No change	No change
12	API+ Crospovidone	5:1	Off white	No change	No change
13	API+ Sodium starch glycolate	5:1	Off White	No Change	No Change
14	API+ Advantia Prime Pink	5:1	Light Brown	No Change	No Change

Inference: By the physical examination of the mixture of excipient, it was observed that there is no change in the colour of the mixtures even after 4 weeks. So it indicates that there are no interactions between drug and excipients.

COMPATIBILITY STUDY SPECIFICATIONS

Table 15: Specifications of the relative substances

RELATIVE SUBSTANCE	SPECIFICATIONS (%)
Impurity A	NMT 0.2%
Impurity B	NMT 0.2%
Impurity C	NMT 0.2%
Highest unknown impurity	NMT 0.2%
Total impurity	NMT 1.5%

Table 16: Relative substances in Sorafenib tosylate

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.016	0.016	0.023
Impurity B	ND	ND	ND
Impurity C	0.050	0.056	0.056
Highest unknown impurity	0.013	0.012	0.012
Total impurity	0.079	0.084	0.091

Table 17: Relative substances in Sorafenib +Micro Crystalline Cellulose

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.014	0.017	0.015
Impurity B	ND	ND	ND
Impurity C	0.043	0.043	0.041
Highest unknown impurity	0.009	0.011	0.009
Total impurity	0.071	0.073	0.065

Table 18: Relative substances in Sorafenib + Croscarmellose sodium

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.014	0.015	0.016
Impurity B	ND	ND	ND
Impurity C	0.045	0.045	0.043
Highest unknown impurity	0.013	0.011	0.010
Total impurity	0.072	0.074	0.069

Table 19: Relative substances in Sorafenib + Sodium Lauryl Sulfate

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.017	0.019	0.019
Impurity B	ND	ND	ND
Impurity C	0.042	0.049	0.067
Highest unknown impurity	0.013	0.011	0.011
Total impurity	0.072	0.083	0.097

Table 20: Relative substances in Sorafenib + HPMC E5

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.014	0.021	0.020
Impurity B	ND	ND	ND
Impurity C	0.045	0.049	0.051
Highest unknown impurity	0.011	0.012	0.012
Total impurity	0.070	0.086	0.083

Table 21: Relative substances in Sorafenib + Magnesium Stearate

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.019	0.020	0.019
Impurity B	ND	ND	ND
Impurity C	0.055	0.053	0.052
Highest unknown impurity	0.012	0.012	0.012
Total impurity	0.084	0.091	0.083

Table 22: Relative substances in Sorafenib + Advantia Prime Pink

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.018	0.015	0.019
Impurity B	ND	ND	ND
Impurity C	0.052	0.052	0.050
Highest unknown impurity	0.012	0.013	0.012
Total impurity	0.082	0.085	0.081

Table 23: Relative substances in Sorafenib + Sodium Starch Glycolate

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.24	0.26	0.25
Impurity B	ND	ND	ND
Impurity C	0.40	0.43	0.40
Highest unknown impurity	0.012	0.011	0.009
Total impurity	0.076	0.078	0.072

Table 24: Relative substances in Sorafenib + Crospovidone

RELATIVE SUBSTANCE	INITIAL	14 DAYS	28 DAYS
Impurity A	0.25	0.26	0.28
Impurity B	ND	ND	ND
Impurity C	0.046	0.046	0.044
Highest unknown impurity	0.013	0.012	0.010
Total impurity	0.074	0.075	0.070

Impurity A: 4-(2-(N-methyl carbonyl)-4-pyrydyloxy) aniline.

Impurity B: 1, 3-Bis (4-chloro-3-di floro phenyl) phenyl urea

Impurity C: 4 (4- ((((2-chloro-3-tri floro methyl) phenyl) amino) carbonyl) amino)-phenyl)-N-methyl-2-pyridine carboxamide tosylate.

Discussion:

The increase in impurities at the initial stage is found in sodium starch glycolate and Crospovidone. So these are incompatible with active ingredient. Hence, it is recommended that the above excipients cannot be used in further formulation development trials.

Calibration of Standard Graph of Sorafenib Tosylate:

Standard graph of Sorafenib :

The construction of standard calibration curve of Sorafenib tosylate was done by using 0.1M Hydrochloric acid as the medium. From the stock solution, calibration standards were prepared by adding different concentration of the sorafenib solution and volume made with the mobile phase to yield the final respective concentration of 6.55, 10.48, 11.79, 13.1, 14.41, 15.92 and 19.65 µg/ml. The standard solutions were injected separately and the chromatogram was recorded using a UV detector at 293 nm. The standard graph of Sorafenib tosylate was constructed by taking the peak area on Y-axis and concentrations on X-axis.

Table 25: Peak area responses of Sorafenib tosylate.

S.no	% Level	Concentration(µg/ml)	Peak Area
1	**50**	6.55	193481
2	80	10.48	309568
3	90	11.79	348265
4	**100**	13.10	386961
5	110	14.41	425657
6	120	15.72	464353
7	**150**	19.65	580442

Standard graph of Sorafenib:

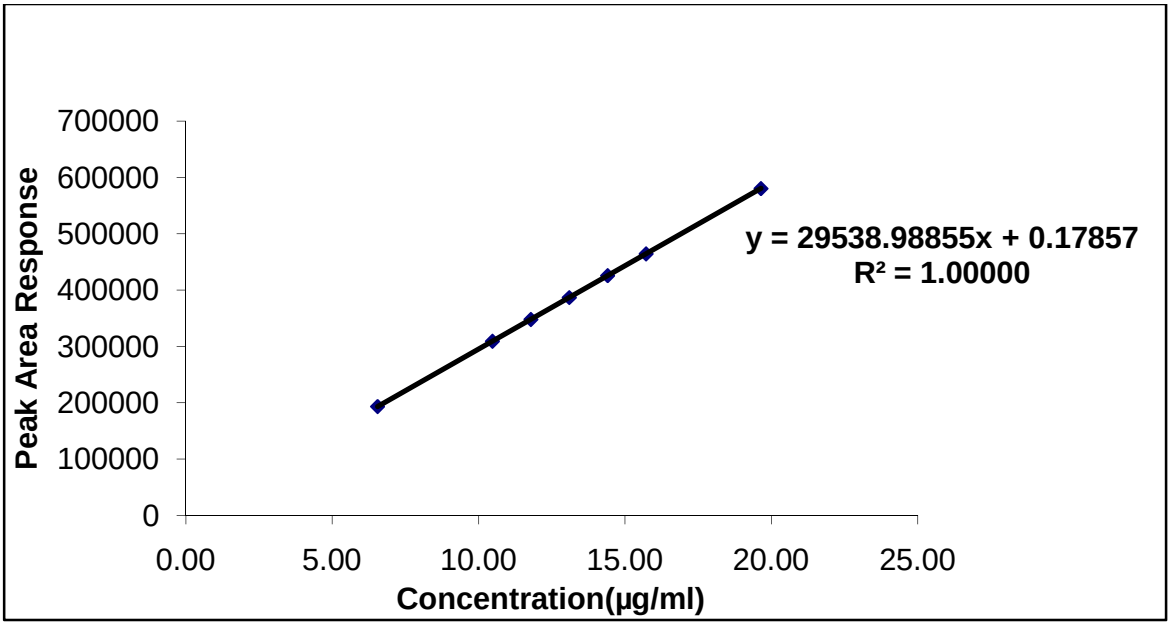


Fig. 5. Standard graph of Sorafenib.

Evaluation of the Prepared Tablets for Physical Parameters:

All formulations were tested for Physical parameters like hardness, thickness, weight variation, friability and found to be within the Pharmacopoeial limits. The results of the tests were tabulated. The drug content of all the formulations was determined and was found to be within the permissible limit. This study indicated that all the prepared formulations were good.

Table 26: Results for evaluation parameters of all formulations

S.No	Formulations	Thickness (mm)	Hardness (kg/cm^2)	Disintegration (Min)	Friability (%)	Assay (%)
1	F-1	5.5±0.4	8.9±1.4	9.29	0.08	97.3
2	F-2	4.62±0.016	15.1±0.03	9.02	0.06	97.5
3	**F-3**	**5.45 ±0.024**	**13.4 ±0.51**	**5.53**	**0.15**	**99.9**
4	F-4	4.86 ±0.035	14.19±0.22	8.5	0.09	94.1
5	F-5	4.9± 0.016	14.1 ± 0.27	18	0.1	98.2
6	F-6	4.67 ±0.052	14.78±0.59	20	0.08	92.4
7	F-7	5.42 ±0.022	13.6±0.47	5.7	0.16	99.7
8	F-8	5.64 ±0.019	13.4 ± 0.35	5.42	0.14	98.5
9	F-9	4.86 ±0.035	14.19±0.22	8.5	0.09	94.1
10	F-10	5.82± 0.029	13.04±0.49	15	0.18	97.4
11	F-11	5.07 ±0.053	14.46±0.32	8.29	0.09	98.3
12	**Innovator**	**5.44 ± 0.04**	**13.5 ± 0.51**	**5.55**	**0.15**	**98.8**

ASSAY(by HPLC):

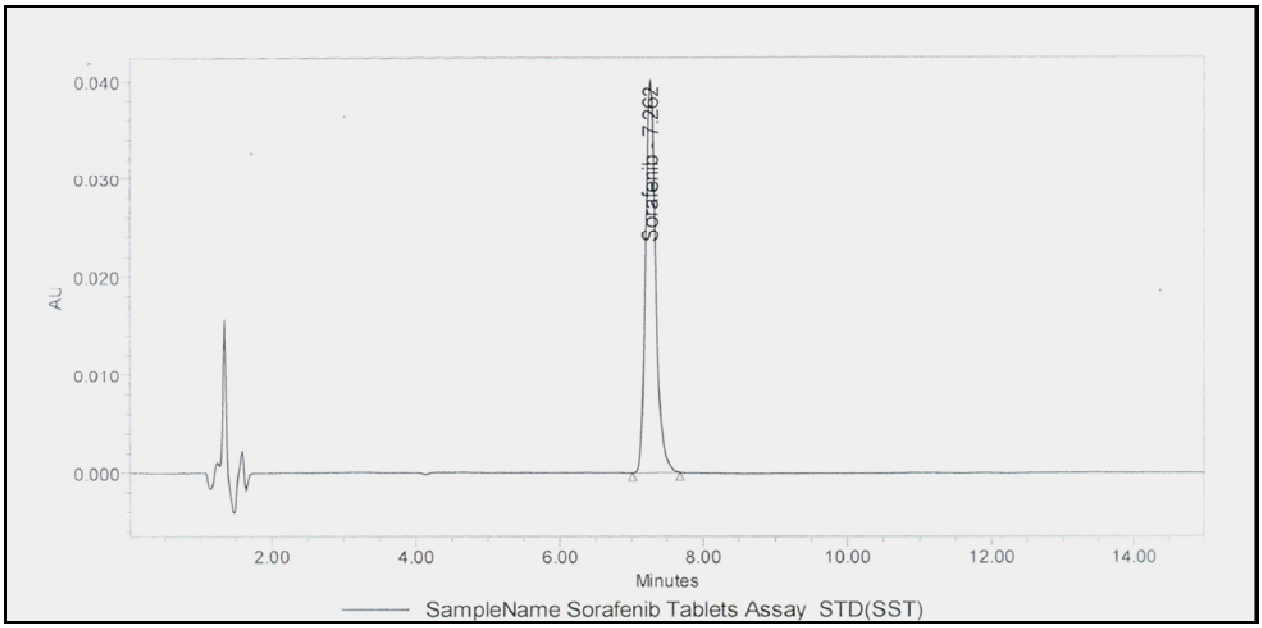


Fig. 6. Chromatogram of Sorafenib tosylate standard preparation

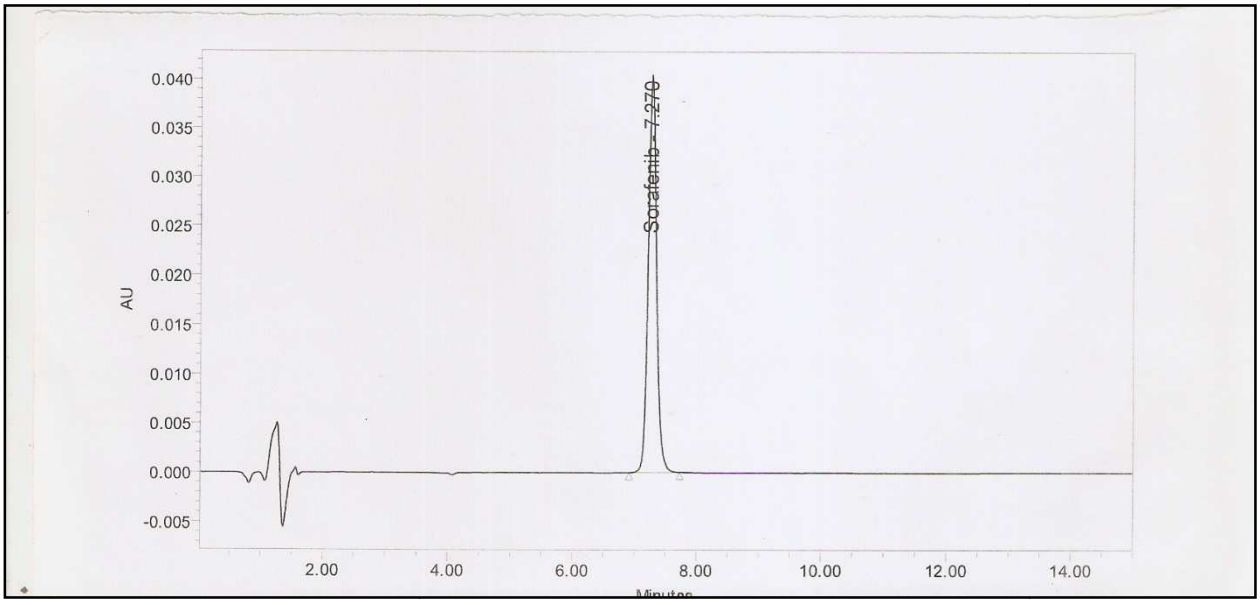


Fig. 7 . Chromatogram of Sorafenib tosylate in sample preparation

Inference: Sorafenib assay was carried by HPLC method by using UV-detectors. The above chromatograms are indicating Sample and Standard chromatograms respectively. Content uniformity was calculated from the above chromatograms peak area responses.

***In vitro* Dissolution studies:**

The dissolution conditions used for studying the drug release from tablet of Sorafenib tosylate are:

Apparatus	: USP apparatus II (Paddle)
Agitation speed (rpm)	: 75 rpm
Medium	: 0.1N HCl with 1%SDS
Volume	: 900 ml
Temperature	: 37.0 ± 0.5° C
Time	: 5, 10, 15, 20 and 30 min.

Results of Dissolution profile:

Table 27: Cumulative % drug release of different formulation

S.No	Time	F- 3	F-4	F-5	F-6	F-7	F-8	F-9	F-10	F-11	Innovator
1	0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	0	0	**0**
2	5	75.2	70	71.6	60.4	72.2	73.15	50.5	72.8	73.4	**73.80**
3	10	87.5	75.2	77.8	62.2	78.4	78.3	55.2	80.5	78.6	**88.70**
4	15	95.8	82.3	81.2	70.1	86.9	83.1	70.3	87.2	85.3	**92.30**
5	20	97.5	88.9	87.4	75.2	90.5	89.9	72.5	90.4	89.2	**93.80**
6	30	97.7	92	92.7	78.6	96.10	94.10	75.1	93.40	92.8	**94.90**

F - 3 as the best formulation as it showed total drug release with in 30 min than all other formulations when compared to the reference product.

Comparision of dissolution profile:

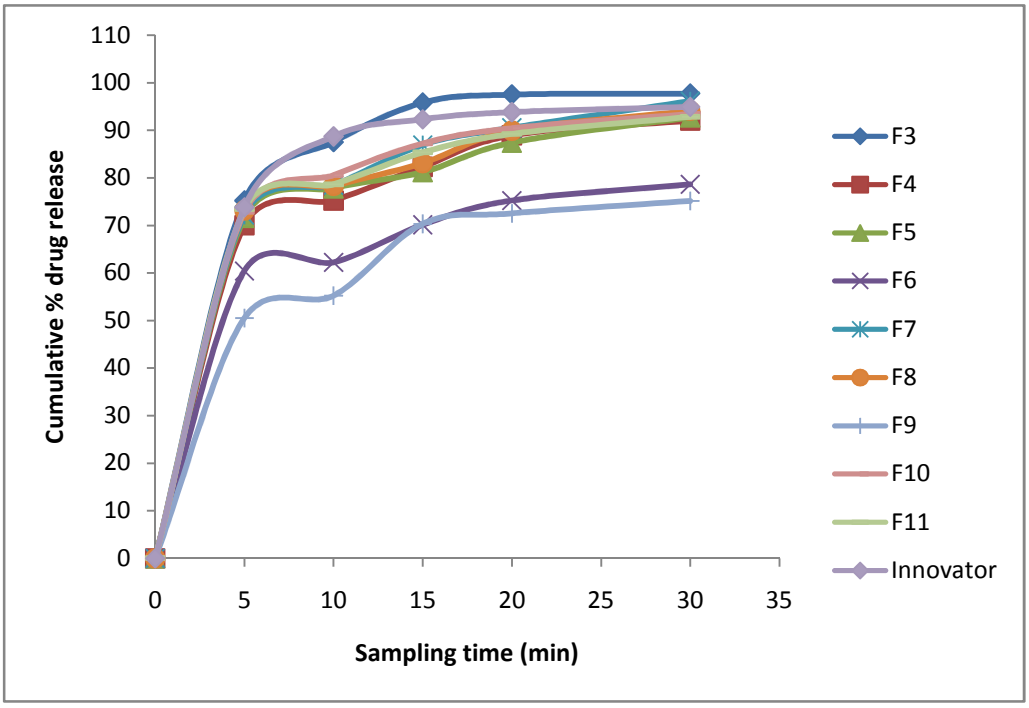


Fig. 8. Comparative *in vitro* dissolution studies with innovator product

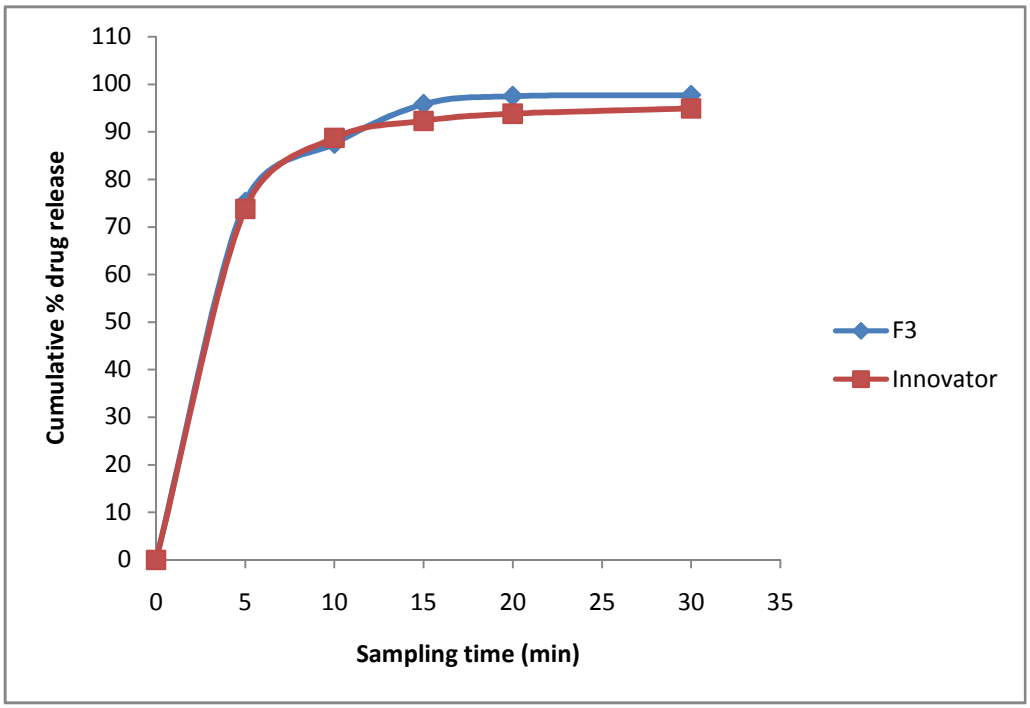


Fig. 9. Comparative dissolution profile for optimized and reference product

Inference: Among the all formulations, formulation 3 shows best dissolution profile, when compared to other formulations. This is because of use of 10% concentration of super disintegrant, croscarmellose act by swelling mechanism. Hence these mechanism aids in the faster release of the drug from the dosage form. Comparative i*n vitro* dissolution studies were carried out in which optimized formula was compared with Innovator product (Nexavar). It was found that optimized formula has shown better dissolution profile than marketed product.

Kinetic release Profile Modeling:

Regression coefficient (R^2) values for different kinetic models for all formulations.

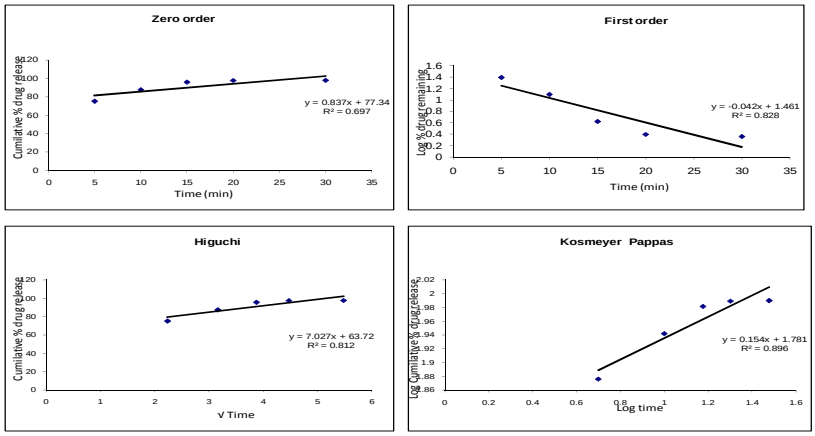


Fig. 10. Graphical representation of kinetic modelings for optimized formulation.

It was found out that the optimized formulation was best explained by korsmeyer peppas Model (R^2 = 0.896), then first order (R^2 = 0.824) followed by Higuchi Model (R^2 = 0.812) and Zero order (R^2 = 0.697). This explains why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred to as square root kinetics (or Higuchi's Kinetics). Further, in the dissolution profile it was noted that the maximum release of the drug occurred at 15 minutes and followed the first order kinetics, where as in the graphical calculation, the regression co efficient for the korsmeyer pappas exhibited the maximum regression value. This may be due to the sink level saturation within 15 minutes.

Stability studies

The optimized tablets from batch F3 were charged for stability studies at 40^0C and 75% RH. There was no change in physical appearance, color. Formulations were analyzed at the end of 3 months for general tablet properties like hardness, friability, drug content and dissolution studies. Tablets have shown no much deviation in hardness, friability values. And Average drug content of the tablets were found to be 99.5±0.4% of the labeled claim. In vitro dissolution profile showed that there was no significant change in the release rate of the drug from optimized tablets at the end of 6 months.

Table 28. Stability data for optimized tablets

Characteristics	Initial	1st month	2nd month	3rd month	6th month
Water content	1.826%	2.64%	2.77%	3.352%	3.3%
Content uniformity	99.8%	99.72%	99.7%	99.7%	99.68%
% Friability	0.15	0.15	0.15	0.15	0.15
Hardness (kg/cm^2)	8.9	8.9	8.9	8.9	8.9
Disintegration time	5min 20 sec	5 min 20sec	5min 25sec	5min 27 sec	5 min 30sec

Table 29. Stability study data (Accelerated) of trial F – 03:

S.No	Parameters		Specifications	Test Condition			
				40 ± 2^{0}C & 75 ± 5% RH			
				0 Day	1	2	3
1	Description		Pink coloured round shaped film coated tablet.	Comply	Comply	Comply	Comply
2	Moisture content		Not more than 5.0%	1.826%	1.953%	2.297%	2.16%
3	Assay		NLS 90% &NMT 110%of labeled amount of drug.	99.6%	99.1%	100.8%	99.5%
4	Related substances by HPLC	I.Unknown individual impurity maximum	NMT 0.2%	0.08%	0.008%	0.006%	0.023%
		II.Total impurity	NMT 2%	0.054%	0.055%	0.053%	0.090%
5	Dissolution		NLT 80% of labeled amount of sorafenib dissolved in 30 min	95.5%	85.9%	85.8%	81.8%

Table 30. Stability study data (long term data) of trial F – 03:

S.No	Parameters		Specifications	Test Condition			
				25 ± 2^{0}C & 60± 5% RH			
				0 Day	**1**	**2**	**3**
1	Description		Pink coloured round shaped film coated tablet.	Comply	Comply	Comply	Comply
2	Moisture content		Not more than 5.0%	1.826%	1.947%	2.233%	2.218%
3	Assay		NLS 90% &NMT 110%of labeled amount of drug.	99.6%	100.0%	100.3%	99.2%
4	Related substances by HPLC	I. Unknown individual	NMT 0.2%	0.008%	0.008%	0.007%	0.044%
		II.Total impurity	NMT1.5%	0.054%	0.059%	0.056%	0.099%
5	Dissolution		NLT 80% of labeled amount of sorafenib dissolved in 30 min	95.5%	99.9%	99.5%	100.7%

Table 31. Comparison of drug release profile of initial and stability batches

Time Points	Initial	1st month	2nd month	3rd month	6th month
5 min	97.2%	96.5%	96.2%	95.8%	94.3%
10 min	99.25%	97.6%	96.9%	96.1%	95.4%
15 min	100.1%	98.3%	97.8%	97.5%	96.3%
20 min	100.2%	99.1%	98.6%	98.3%	97.1%
30 min	100.3%	99.9%	99.5%	98.9%	98%

Stability profile of Optimized formula

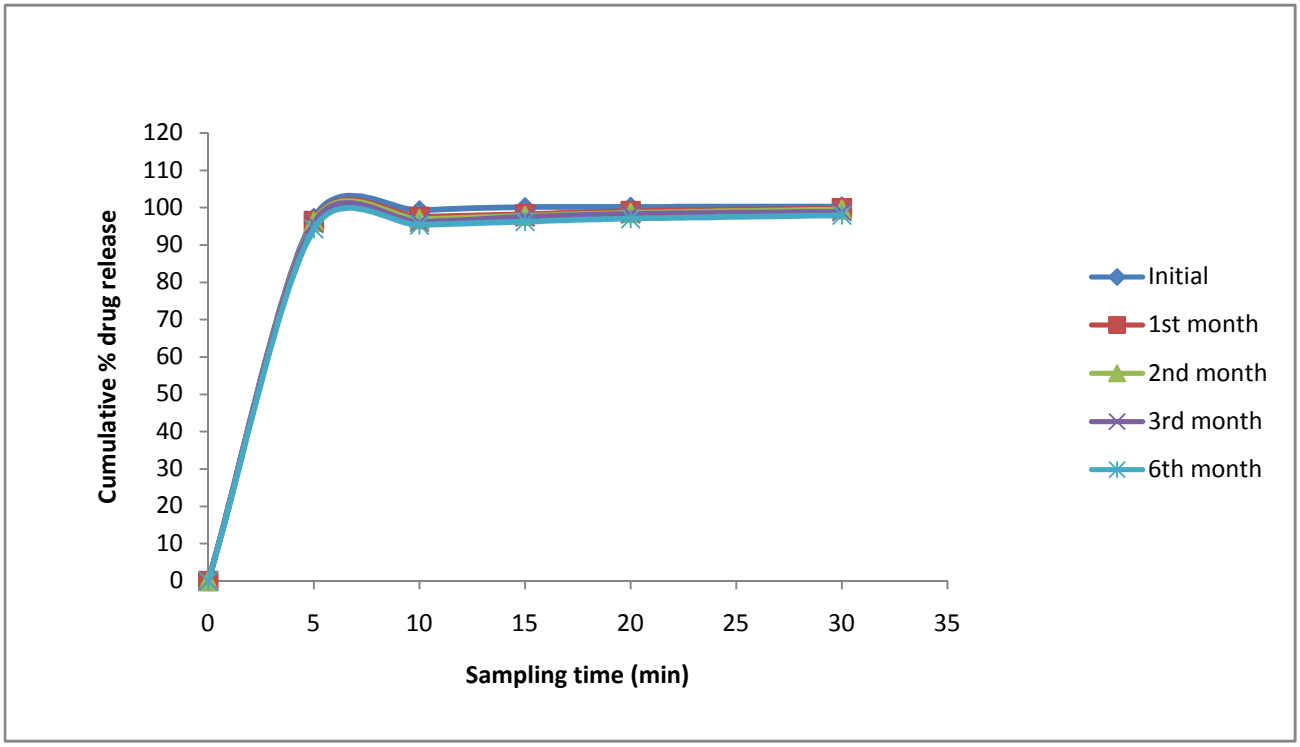


Fig. 11. Comparison of dissolution profile for stability batches

Conclusion: Stability studies for the optimized tablets was carried out at different temperatures and relative humidity of $40^0C \pm 2^0C$, 75%±5% RH and 25^0 C $\pm 2^0$ C, 60%±5% RH for a period of six months. Tablets are evaluated for physical appearance, colour, hardness, friability, drug content and dissolution studies. Tablets have not shown any significant change during storage. Hence it was concluded that the optimized tablets have the good stability during their shelf life.

The objective of the present study was to design and develop a oral solid dosage form of low cost generic version Sorafenib tosylate film coated tablets with an aim to improve the bioavailability. Sorafenib tosylate is a antineoplastic agent having low bioavailability (25-49%), hence needed to be administered two times in a day to achieve therapeutic concentration level.

Systematic studies were conducted using different polymers in different concentrations to prepare Sorafenib tosylate tablets. All the prepared systems were evaluated for the different parameters. Before the preparation of tablets, preformulation studies were conducted like drug-excipients stability studies to find out the interaction, micromeritic properties to assess flowability, compressibility and solubility. All the formulations gave good results for above preformulation studies.

Formulated tablets gave satisfactory results for various physical tablet evaluation parameters like tablet dimensions, hardness, friability, weight variation and content uniformity and were found within the permissible range.

Then prepared tablets were evaluated for *in vitro* drug release. In the present study, croscarmellose, crospovidone and sodium starch glycolate were used as disintegrants. Comparing these three disintegrants, it was found that the formulation containing croscarmellose has showed best dissolution profile.

Drug release profiles are fitted to kinetic modelings like zero order, first order, Higuchi model and Korsemeyer Peppas models. In the dissolution profile, it was noted that the maximum release of the drug (95.8%) occurred at 15 minutes and followed the first order kinetics, where as in the graphical calculation, the regression coefficient for the Korsmeyer Peppas exhibited the maximum regression value. This may be due to the sink level saturation within 15 minutes. Stability studies were conducted for optimized formulation at 25°C with 60% RH and 40°C 75% RH, and the formulation is found stable for all evaluation parameters.

Finally it was concluded that:

Formulation 1, which was prepared by direct compression method has shown poor flow properties and failed to achieve better dissolution profile.

Formulation 2 was prepared by the method of slugging has shown poor flow properties and sticking was observed during compression because of low fill weight, so the dissolution test was failed.

Formulation 3 to 8 was prepared by the method of wet granulation with varying disintegrants like Croscarmellose, Crospovidone and Sodium starch glycolate in different concentrations. Formulation 3 prepared by using Croscarmellose in the concentration of 10% and SLS in the concentration of 2%, where tablets are film coated to increase the elegance and to give a good appeal, showed a better disintegration time and dissolution.

To improve the dissolution of the drug, formulation 4 and 5 an attempt was made by using a 10% concentration of crospovidone and 10% concentration of sodium starch glycolte as disintegrants and they failed to show the disintegration time less than 30 min as per USP and they were also failed in stability. Hence formulation 6,7 and 8 was prepared by using Croscarmellose as disintegrant with 8%,12% and 14% concentrations. The disintegration time of formulation 6 was not under the specified limits, but formulations 7 and 8 showed a better dissolution profile.

F9, F10, F11 formulation were prepared by using sodium lauryl sulphate in different concentrations of 1%, 3% and 4%. Among the three formulations F9 showed the drug release less than 70% which was not under the specified limits, where as F10 and F11 were found to exhibit a good dissolution profile. The formulations which exhibited good dissolution profile were selected for comparison with the reference product. Comparing these formulations it was found that F3 was found to match the reference product. Hence stability studies were performed for this batch (F3) under accelerated and long term testing conditions. The product was also analyzed for physical appearance, moisture content, assay, related substances and dissolution. The results obtained were found to be within the specified limits.

The bigger scale confirmatory batch for the above said formulation (F12) was made and it is kept for 6 months accelerated stability studies and based on the result, a pilot scale will be executed.

Conclusion:

Sorafenib tablets were prepared by direct compression, slugging and wet granulation method. From the results obtained it was found that the wet granulation method was found to be better when compared with the other two methods, since it exhibited a better dissolution profile matching the innovator product. Further, the drug release of the optimized formulation was found to be more than the reference product at the end of 30 minutes.

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